The Developmental Origins of Children's Energy Balance-Related Behavior and Physical Fitness

van Deutekom, A.W.

2017

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THE DEVELOPMENTAL ORIGINS OF CHILDREN'S ENERGY BALANCE-RELATED BEHAVIOR AND PHYSICAL FITNESS

Arend Willem van Deutekom

The studies performed in this thesis were financially supported by the Netherlands Organization for Health Research and Development (ZonMw), The Hague, The Netherlands.

Financial support for publication of this thesis was generously provided by Stichting Researchfonds Kindergeneeskunde VUmc, the Netherlands Organization for Health Research and Development and Abbott/St Jude Medical, Veenendaal, the Netherlands.

Cover: Raphael Bartels, http://www.raphaelbartels.com;
Lay-out: Design Your Thesis, http://www.designyourthesis.com;
Printing: Ridderprint BV, the Netherlands.

ISBN: 978-94-6299-530-7

Common sense is just a matter of statistics

George Orwell in *Nineteen Eighty-Four*

Opgedragen aan mijn ouders

VRIJE UNIVERSITEIT

THE DEVELOPMENTAL ORIGINS OF CHILDREN'S ENERGY BALANCE-RELATED BEHAVIOR AND PHYSICAL FITNESS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. F.A. van der Duijn Schouten,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op vrijdag 21 april 2017 om 9.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Arend Willem van Deutekom
geboren te Amsterdam

Promotoren:	prof.dr. R.J.B.J. Gemke prof.dr. M.J.M. Chin A Paw
Co-promotor:	dr. T.G.M. Vrijkotte

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LIST OF ABBREVIATIONS

20-m MSRT	20 meter multistage shuttle run test,
ABCD	Amsterdam Born Children and their Development,
ANS	Autonomic nervous system,
BIA	Bioelectrical impedance analysis,
BMI	Body mass index,
CEBQ	Child Eating Behavior Questionnaire,
CLASS	Children's Leisure Activities Study Survey,
c.p.m.	Counts per minute,
CVD	Cardiovascular disease,
DOHaD	Developmental Origins of Health and Disease,
DP	Diastolic pressure,
DXA	Dual energy X-ray absorptiometry,
FFQ	Food Frequency Questionnaire,
kcal	Kilocalories,
kg	Kilograms,
MAP	Mean arterial pressure,
MET	Metabolic equivalent units,
MVPA	Moderate-to-vigorous physical activity,
PA	Physical activity,
PAQ-C	Physical Activity Questionnaire for Older Children,
PEP	Pre-ejection period,
PNS	Parasympathetic nervous system,
RSA	Respiratory sinus arrhythmia,
SB	Sedentary behavior,
SBJ	Standing broad jump,
SD	Standard deviation,
SDS	Standard deviation score,
SES	Socio-economic status,
SNS	Sympathetic nervous system,
SP	Systolic pressure,
WHO	World Health Organization.

1. GENERAL INTRODUCTION

THE OBESITY PANDEMIC

The rising prevalence of overweight and obesity in children and adults worldwide is considered a global pandemic[1], and the World Health Organization (WHO) calls childhood obesity one of the most serious public health challenges of the 21st century.[2] Since 1980, overweight and obesity rates have increased dramatically. The 2013 Global Burden of Disease Study estimated that 2.1 billion people are overweight globally, which equates to 38% of the world population, and a rise of 28% in adults and of 47% in children.[3] Overweight and obesity were estimated to cause 3.4 million deaths annually, 4% of years of life lost, and 4% of disability-adjusted life-years worldwide.[4] Data from studies in the USA have suggested that, unabated, the current obesity prevalence could lead to future falls in life expectancy.[5] Childhood obesity increased substantially, with 23% of the American children now being overweight or obese.[3] In the Netherlands, 12% of the children were overweight in 2015.[6] Although this suggests a decrease in childhood obesity rates since 1999, its prevalence remains historically high, there are widening inequalities between ethnic groups and it is still a so-called time bomb for future demands on health services.[6, 7] Concern about the health risks associated with rising obesity rates has become nearly universal, but beyond acknowledgment that there is a worldwide problem with far-reaching consequences for health and wellbeing, little progress has been made tackling the problem.[8]

The target of the WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases is to "halt the rise in obesity between 2010 and 2025".[9] This obesity target of no increase appears modest, yet, achievement of this seemingly low bar is probably the most challenging of the WHO targets. These targets will not be achieved without a better understanding of the underlying drivers of the obesity pandemic. The currently dominant scientific and public health model assumes that the current obesity pandemic is a function of individual energy imbalances where energy consumed exceeds energy expended, dichotomizing its cause into 'a relative overconsumption of food' versus 'a relative lack of physical activity'.[10] Although fundamentally correct, this energy balance concept oversimplifies the pathogenesis of obesity.[11] Instead, obesity is the consequence of interplay between a wide variety of variables and determinants related to individual (epi-)genetic, cellular, neuroendocrine and behavioral factors, set within a social, cultural and environmental landscape (figure 1.1.).[12,13]

It is increasingly being recognized that the processes underlying an individual's propensity for obesity originate early in life, even before birth, long before obesity and associated diseases occur. The importance of these developmental processes in early life were acknowledged in a special high level meeting on obesity of the United Nations General

Assembly in September 2011, since ". . .maternal and child health is inextricably linked with obesity and its risk factors. . .". [14] This statement represented a substantial change in focus from the earlier public health policies, reflecting the acceptance of the field of biomedical science and public health of non-communicable diseases, that has become known as the Developmental Origins of Health and Disease (DOHaD).

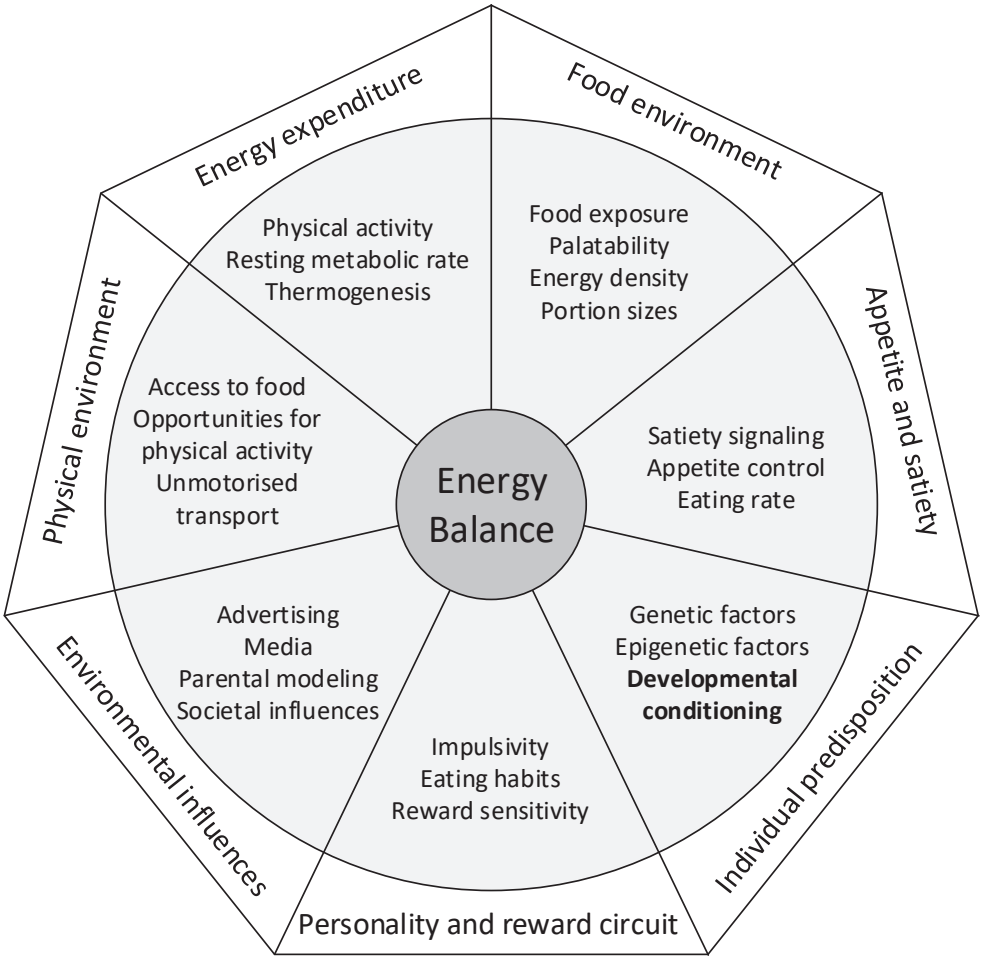

Figure 1.1 Schematic overview of the determinants of the energy balance. The outer ring represents the major classes of determinants, the inner ring some of the individual determinants in each class. The data on which the figure is based come from the Obesity Systems Map introduced by the UK Foresight programme, a multidisciplinary effort to plan the governmental response to obesity.[12]

THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

The DOHaD hypothesis proposes that environmental exposures, acting at different stages of fetal and early postnatal development, lead to permanent adaptations in the structure, physiology and function of various organ systems. It allows an organism to change its phenotypic development from that of its evolved lineage in response to an experienced or anticipated environmental change, which can potentially confer adaptive benefit later. For example, if in utero nutrition is compromised, the developing fetus detects this poor nutritional environment and uses this as a cue for the induction of 'predictive adaptive responses' in neuroendocrine regulatory systems and metabolic pathways to maximize uptake and conservation of any nutrients available, resulting in a conservative metabolism. This anticipation of a scarce nutritional environment may confer potential adaptive value. The problems arise, however, where postnatal nutrition is adequate or plentiful and exceeds the range of the predictive adaptive responses. The consequence of this, it is proposed, is development of obesity and associated diseases.[15, 16]

The concept that early life influences produce long-term effects on health and disease was already appreciated in the writings of Hippocrates and Freud.[17] But the greatest impulse to the DOHaD hypothesis came from the series of epidemiological studies by Barker and colleagues from 1986 onwards.[18-21] In Barker's studies links were established between low birth weight, weight at 1 year of age, and higher prevalences of hypertension, coronary heart disease, stroke, and metabolic syndrome in adulthood. A plethora of epidemiological studies has substantiated this relationship between low birth weight, as a reflection of poor fetal nutrition, and the development of adult diseases such as ischemic heart disease[22], stroke[23], insulin resistance and type 2 diabetes[24], but also central adiposity[25], reduced adult bone density[26], schizophrenia[27] and asthma and atopic conditions.[28] This concept has been replicated in large cohorts from many populations.[29-31] These studies not only confirmed that adult disease risk was affected by early influences, but also that this risk was graded across the entire range of early development. Of key importance from a public health perspective was the finding that this included subjects whose birth weight was unequivocally within the normal range, rather than being a pathological feature which is expressed below some critical cut-off point. More recent studies confirm the graded nature of the phenomenon, and for a wider set of processes such as neurocognitive development.[32]

The epidemiological work is given support by two other lines of evidence. First, studies on the consequences of historical events such as war have shown that extreme changes in the developmental environment modulate later disease risk. During the Dutch famine in the winter of 1944–1945, food supply to the Western part of the Netherlands was cut

dramatically (with reported daily intake falling to 400–800 kilocalories). Antenatal exposure to the famine, at least in the third trimester of pregnancy, was associated with a low birth weight and a decreased glucose tolerance at the age of 50 compared to individuals born the year before or after the famine.[33] Subsequent studies of this population found that exposure to famine in early gestation was associated with a more atherogenic lipid profile[34] and a higher risk of coronary heart disease in adulthood[35], but evidence is inconsistent in relation to whether fetal exposure to famine was associated with elevated blood pressure.[36, 37]

Second, a wide range of animal models have confirmed that developmental processes occur in response to early external influences. Initially most animal studies involved investigation of maternal undernutrition during gestation and the cardiometabolic effects, such as adiposity and blood pressure, in the offspring.[38] The most commonly used challenge was a low-protein diet fed to the mother during pregnancy. This produced low birth weight and produced effects on offspring blood pressure[39], cardiovascular function[40, 41] and body composition.[42, 43] The animal models used included the rat, mouse, guinea pig, sheep, pig, and non-human primate, and in each the DOHaD concept has been confirmed.

It has only relatively recently been realized that the DOHaD concept also operates in the context of a prenatally or neonatally excessive nutritional environment, leading to either high birth weight or accelerated infant weight gain.[44] Early evidence of this comes from the 1946 United Kingdom birth cohort[45] and from the meta-analysis of the Nordic cohorts[30] which show a U-shaped relation between birth weight and blood pressure. Children showing accelerated growth in early infancy and childhood are at greater risk of adulthood cardiovascular disease, especially if they were small at birth.[46] Also in preterm-born infants, rapid postnatal growth is associated with risk factors for cardiovascular disease in adolescence.[47] Rapid weight gain in infancy is associated with childhood[48, 49] and adolescent[50] obesity and with childhood cardiovascular dysfunction.[51] The underlying concept is that infant formula feeding and energy-dense processed foods are evolutionary novelties, qualitatively very different from the historical nutritional (breastfed) environment, and thus a mismatch is likely between the diet predicted and diet consumed.[16] Although this is a different mechanism than the predictive adaptive responses elicited by perinatal nutritional deprivation, there is a striking consistency in the adult phenotype, involving physiological systems aimed at gaining weight, a less favorable body composition, a tendency for high blood pressure and obesity, and a higher risk of cardiovascular disease.

How long after birth developmental effects can be induced in humans is an open question, but it is clear that they can persist through infancy. It has been argued that it is the timing of the 'obesity rebound' in childhood rather than the nutritional influences in infancy that induces metabolic conditioning.[52] Certain growth trajectories in childhood clearly produce sustained metabolic effects in the adult, indicating that the window in which nutrition affects later health may extend well into childhood.[53]

UNDERLYING DOHAD

Now that the DOHaD concept becomes generally acknowledged and incorporated in public health policies, research has shifted from the study of simple associations between early life events and subsequent pathology to the investigation of underlying mechanisms. Again, animal models provided a fundamental contribution by focusing on the pathways involved. In detailed animal investigations, it was possible to define and control the stimulus used to induce the response, and to measure that response in a range of tissues and at various stages during development and throughout the life-course.[54-56] This led to new insights into developmental effects on tissues, organs, and systems, and how these effects form part of an integrated physiological response of the organism to developmental signals. These studies suggested that the processes we appreciate to underlie DOHaD also include the adaptation of behaviors closely related to the energy balance. For example, an experiment in which pregnant rats were fed a restricted diet, and their offspring fed a high-fat diet, was shown to affect behavioral components such as appetite control and voluntary exercise in the offspring.[42, 43] In a second series of rat studies, dietary restrictions in the pregnant mother produced offspring with a preference for a high fat diet and reduced activity levels, especially in female offspring.[57-59] Recently, a mouse model also linked maternal obesity to offspring's behavior. Offspring of obese mice paradoxically had low birth weight, which was followed by reduced activity levels and subsequent obesity in adulthood in females.[60] These sex-specific effects of nutritional modulations during gestation were also clearly highlighted in a meta-analysis on the behavioral effects of gestational nutritional modulation in animals.[61] This study also suggested that effects on behavior are predominantly apparent when gestational nutritional insults are followed by postnatal excessive nutrition, implying that a more important window for altering behavior might be after birth. Experimental brain lesion studies, neuroanatomical studies and gene knockout mouse models further clarified the neuroendocrine pathways involved[62], and confirmed that the hypothalamic circuitry responsible for appetite regulation and the mesolimbic 'reward' pathways associated with behavior are susceptible for perinatal insults, at least in animals.[63]

Clinical evidence for the behavioral alterations produced by early nutritional stimuli first came from the famine studies, showing that adults born during famine had a higher caloric intake, mainly due to a preference for fatty foods, and tended to be less physically active. [64, 65] Clinical studies in very low birth weight subjects found a relationship between low birth weight and less sports participation during adolescence[66, 67] and young adulthood[68], although this may also be the consequence of neurological disabilities or parental overprotection. A meta-analysis of population-based Nordic cohorts suggested an inverse U-shaped relationship of birth weight with physical activity (PA) levels, with lower PA levels in those born in the lower and higher extremes of the normal birth weight range, but older age groups mainly drove this association.[69] A meta-analysis of over 10,000 subjects recently found a small but significant positive association of birth weight with sedentary behavior (SB) in childhood and adolescence.[70] However, these studies all focus on prenatal influences, while there is very little available evidence to determine whether postnatal nutritional cues affect energy balance-related behaviors.[71]

These Developmental Origins of Energy Balance-Related Behaviors may well be one of the mechanisms explaining the perinatal influences on later disease risk, as PA, SB and dietary behaviors are independently linked to several health outcomes, including cardiovascular disease, obesity, cancer and all-cause mortality in adults.[72-76] In children, PA levels are prospectively inversely associated with adiposity[77], although the reciprocal association has also been observed.[78] PA is further positively associated with physical fitness levels[79], and improved PA promotes a healthier cardiovascular risk profile independent of fat mass, including lower blood pressure, higher HDL cholesterol, lower triglycerides, improved glucose tolerance and post-prandial lipidemia.[80, 81] Independent of PA levels, more SB has been associated with the development of obesity in children and adolescents. [76] A recent review of prospective studies, however, found insufficient evidence for an independent association of SB with several cardiovascular health indicators in children, including body mass index.[82]

In addition to PA and SB, there is increasing attention to the early life influences of physical fitness. A number of studies show a positive association between birth weight and later physical fitness levels, which suggests that low birth weight subjects may be at risk to have impaired fitness in later life.[83-85] Neuromuscular fitness (also known as muscle strength) and aerobic fitness (also known as cardiovascular fitness) are main components of physical fitness and strong risk factors for obesity, cardiovascular disease and all-cause mortality.[86] Children and adolescents with higher fitness levels have a healthier cardiovascular profile at these ages and in adulthood[87, 88] and high fitness attenuates the detrimental effect of excessive adiposity on cardiovascular health in childhood[89] and on the risk of becoming overweight in adolescence.[90]

Several neuromuscular and cognitive systems have been suggested to be mediators of the perinatal programming of energy balance-related behavior and physical fitness. One possible mechanism by which the early environment could impact behavior and fitness is the programming of the autonomic nervous system.[91] Crucial for a potential mediating role of the autonomic nervous system is the observation that a permanent increase in sympathetic activity and decrease in parasympathetic activity can be found in animal models of perinatal malnutrition.[92, 93] Additionally, clinical evidence indicates a role for the autonomic nervous system in the development of human behavior, including impulsivity and sensitivity to rewards.[94]

The preliminary evidence reviewed above suggests that energy intake, PA, SB and physical fitness might be parts of the pathway from early life nutrition to adult onset disease, and that autonomic activity mediates this relationship. If future research substantiates these associations, it might have major implications for public health. It suggests that a component of the risk of obesity and cardiovascular disease associated with suboptimal early life growth has a behavioral or fitness element that is potentially amenable to preventive intervention and monitoring. The failure to recognize the pathways of the developmental origins of obesity and to incorporate it into public policy may limit capacity to reduce the escalation of the obesity pandemic.

CONCLUSION

Currently no country has reversed its obesity epidemic, although in the Netherlands the obesity prevalence seems to level off. Extensive experimental animal models and epidemiological evidence have shown that environmental influences during early development affect the risk of obesity and cardiovascular disease in later life. The scarce available studies into the underlying mechanisms indicate that the early life environment might elicit certain behavioral responses, including those related to PA, SB and eating behavior, and changes in physical fitness that may in part explain the higher disease risk. Alterations in autonomic activity may underlie these behavioral responses related to early life nutrition. Unraveling these potential Developmental Origins of Energy Balance-Related Behaviors and Physical Fitness may eventually lead to new public health strategies for identification of groups at risk and prevention.

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2. AIMS, COHORT DESIGN AND OUTLINE OF THE THESIS

AIM OF THE THESIS

As outlined in the introduction (**Chapter 1**), the Developmental Origins of Health and Disease (DOHaD) concept improved our understanding of why some people are more susceptible to obesity and cardiovascular disease than others. Early life induced differences in energy balance-related behaviors, encompassing energy intake, eating behavior, physical activity (PA) and sedentary behavior (SB), and physical fitness may underlie observed associations of early life experiences with adult disease. Understanding these processes underlying DOHaD could potentially guide developing public health policies to identify individuals at high risk of disease and to develop preventative measures to minimize suboptimal energy balance-related behavior and physical fitness induced by early life malnutrition.

The present thesis aims to elucidate the role of prenatal and early postnatal growth, as measured by birth weight and infant growth, respectively, in childhood energy balance-related behaviors and physical fitness. Therefore, we formulated the following research questions:

1. What is the currently available evidence for the association of birth weight and infant growth with energy balance-related behavior in humans?
2. What is the association of birth weight and infant growth with childhood energy intake and eating behavior?
3. What is the association of birth weight and infant growth with childhood PA and SB?
4. What is the association of birth weight and infant growth with childhood physical fitness?
5. Does autonomic nervous system (ANS) activity mediate a potential association of birth weight and infant growth with energy balance-related behaviors in children?

A conceptual framework of this thesis is presented in figure 2.1. These questions will be addressed within the scope of the Amsterdam Born Children and their Development (ABCD) study. The remainder of this chapter describes the general design of the ABCD study, provides some background information on the original cohort and how a subgroup group, in which a detailed assessment of energy balance-related behaviors and physical fitness was conducted, came about. The chapter concludes with the outline of this thesis.

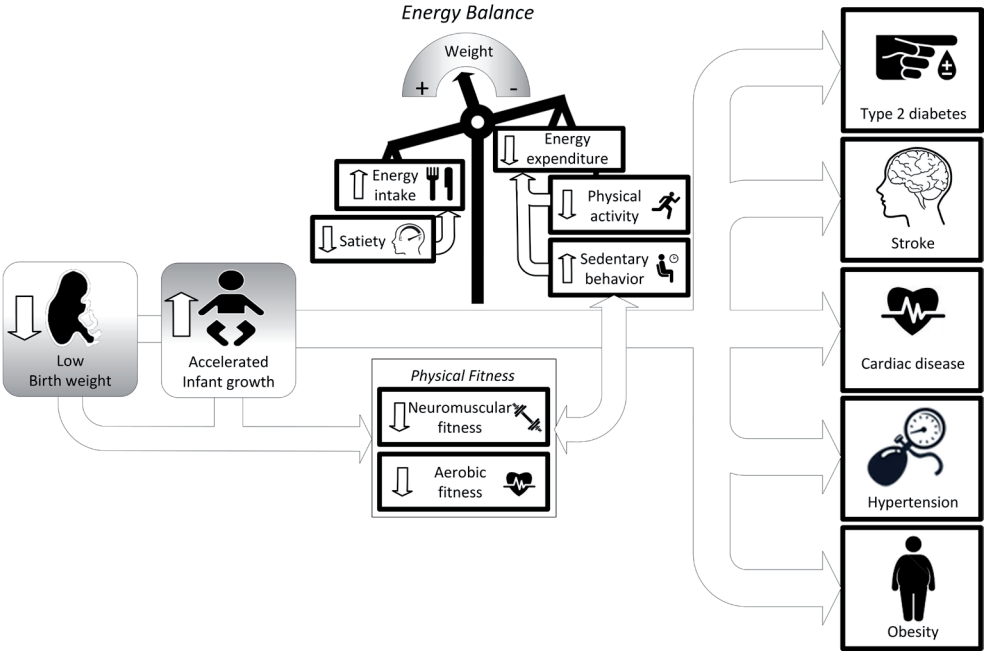

Figure 2.1 Conceptual framework of this thesis depicting the hypothesized mechanisms.

AMSTERDAM BORN CHILDREN AND THEIR DEVELOPMENT STUDY

The ABCD study is a large population-based birth cohort study initiated in 2003 by the Municipal Health Service Amsterdam, the Academic Medical Center and VU University Medical Center. Initially the ABCD study focused on ethnic disparities in children's health at birth as well as in later life, on maternal lifestyle, medical, psychosocial and environmental conditions during pregnancy, and on the extent to which (ethnic disparities in) maternal conditions during pregnancy explain (ethnic disparities in) children's health at birth as well as in later life. However, another focus has been added over the following years, namely to investigate early life conditions and the extent to which these conditions explain children's health in later life.[1] It is the latter focus that forms the basis of this thesis. The sampling procedure and attrition rate of the ABCD study is depicted in figure 2.2.

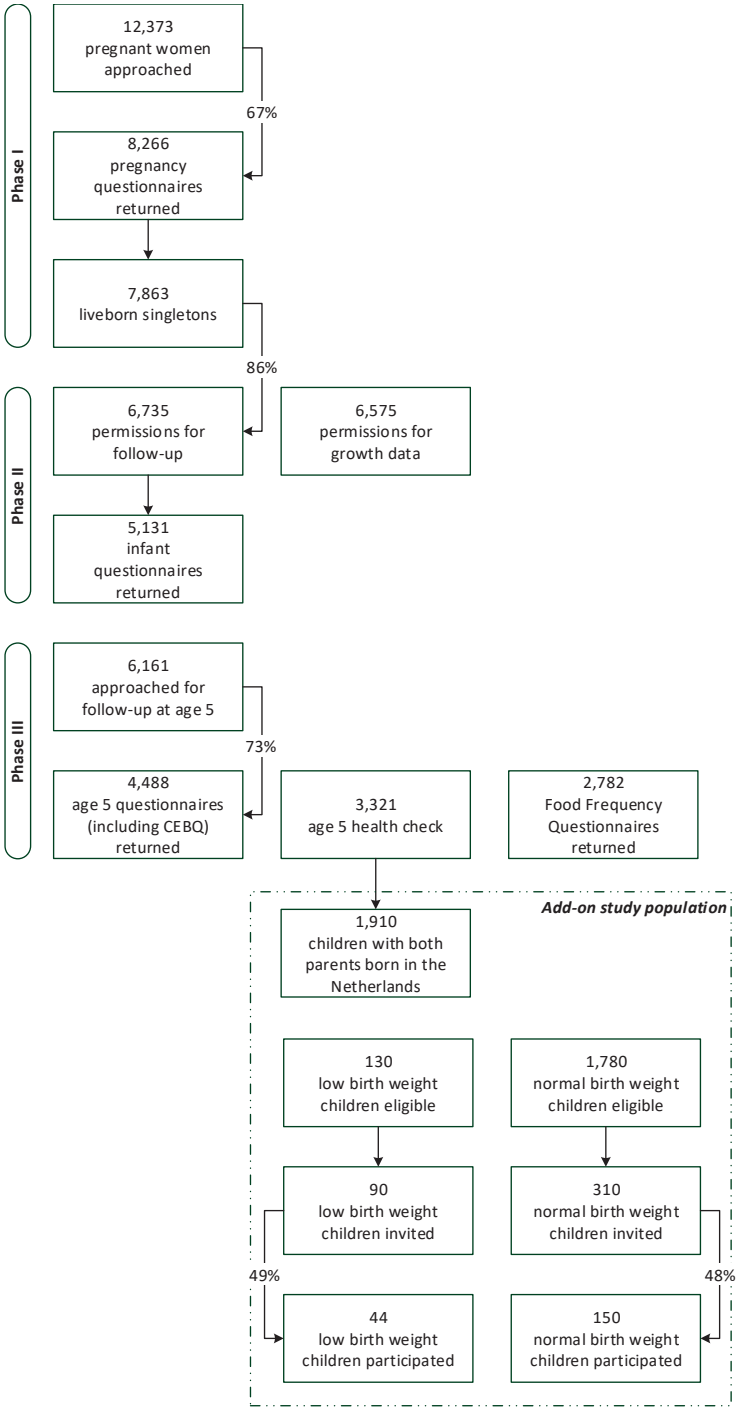

Figure 2.2 sampling procedure and attrition rate of the ABCD study.

Between January 2003 and March 2004, all pregnant women living in Amsterdam were asked to participate in the ABCD study during their first prenatal visit to an obstetric care provider. Altogether, 12,373 women were approached, of which 8,266 (67%) completed the pregnancy questionnaire, covering sociodemographic data, obstetric and medical history and lifestyle and psychosocial conditions. Of this group, 7,863 women gave birth to viable singleton infants. The offspring of these women formed the prenatally recruited birth cohort (Phase I). In the first week after delivery, nurses from the regional vaccine registration (Entadministratie) performed a house visit to obtain a blood sample to screen for congenital metabolic disorders. During this visit, they routinely recorded the date of delivery, infant sex, birth weight and gestational age as provided by the obstetric care provider.

Three months after giving birth, the women who gave permission for follow-up (6,735 mothers of singletons) received a questionnaire concerning the course of their pregnancy and delivery, their lifestyle during and after pregnancy, and the child's health, development, growth and feeding practice (Phase II). In the next four years, specially trained Youth Health Care personnel conducted an average of 14 standardized routine measurements of the children's height and weight to monitor their growth and feeding patterns. Of the 6,735 women who gave birth to live-born singleton infants and permission for follow-up, 6,575 gave permission to collect growth data.

Around their child's fifth birthday, 6,161 mothers were approached for follow-up, consisting of a general questionnaire, a Food Frequency Questionnaire (FFQ) and an 'age 5 health check' (Phase III). The general questionnaire contained questions about the child's health, development and general behavior, as well as items on their child's sports participation, time playing outside and screen time. Four thousand four hundred eighty-eight (73%) mothers completed and returned this questionnaire. The FFQ is a self-administered questionnaire, assessing the child's consumption of 71 food items in the previous four weeks, based on data from the third Dutch National Food Consumption Survey.[2] The FFQ is validated for use in children aged 4–6 years.[2] The 'age 5 health check' consisted of physical measurements, a cognitive test, and the collection of a fasting capillary blood sample to assess blood levels of glucose, total cholesterol, HDL, LDL, triglycerides, and c-peptide. The physical measurements included measurements of anthropometry (height, weight, waist and hip circumference), body composition (fat mass and fat-free mass) by bioelectrical impedance analysis[3], blood pressure, and cardiac activity (heart rate, heart rate variability, and pre-ejection period) using the VU Ambulatory Monitoring System.[4] We assessed cognitive function using four tasks from the Amsterdam Neuropsychological Tasks program.[5] Three thousand three hundred twenty-one children completed the physical examination and in 2,108 children blood samples were collected.

In 2012, when the children were 8-9 years old, we conducted an add-on within the ABCD study for a detailed assessment of the relation of early growth with physical fitness, PA and SB. Of the original ABCD cohort, we randomly selected 400 children of Dutch descent (i.e., with both parents born in the Netherlands) who completed the 'age 5 health check'. Children with a low birth weight had a higher chance of being selected to ensure enough power to detect the anticipated differences in outcome measures between low and normal birth weight children. One hundred ninety-four children participated. In these children, we conducted a detailed assessment of physical fitness levels, PA level and SB. Further details of this subgroup, the background and rationale of the study and the psychometric properties of the conducted tests are discussed in **Chapter 3**.

OUTLINE OF THIS THESIS

After an introduction of the relevance of early life influences to the current obesity pandemic and the potential underlying role of energy balance-related behaviors (**Chapter 1**), a general outline of the ABCD study (**this chapter**) and a detailed profile of the add-on study conducted in 2012 (**Chapter 3**), this thesis continues with the results of a systematic review of the medical literature. In this review, we assess the currently available evidence pertaining to the association of birth weight and infant growth with energy balance-related behaviors, i.e., energy intake, eating behavior, PA and SB, in humans. (**Chapter 4**) We summarize the available evidence through a best-evidence synthesis taking into account the methodological quality of the included studies. The hiatuses in the literature identified by this review are covered in the subsequent chapters.

In a series of original articles, we describe the results of our assessment of the association of birth weight and postnatal growth with different intrinsic features in children of the ABCD cohort, including energy-balance related behaviors, physical fitness and ANS activity. (**Chapter 5, 6, 7 and 8**) These childhood features could all potentially partly explain the association of suboptimal growth in early life with adult disease risk. First, we show how birth weight and postnatal growth are associated with childhood energy intake and eating behavior in the ABCD cohort. (**Chapter 5**) Because data was available for over 3,000 subjects, we were able to provide a detailed account of the individual effects of different periods of postnatal growth, by means of a conditional growth analysis. **Chapter 6** describes the results of our add-on study with regard to PA and SB, in which we assessed the independent contributions of birth weight and infant weight, height and BMI gain on objectively assessed PA and SB at age 8-9. We also assessed the relationship of birth weight and infant growth with physical fitness in this group of children, and present the results in **Chapter 7**. Furthermore, because physical fitness levels are strongly

influenced by the amount of SB and PA participation, we secondarily assessed whether PA or SB mediated the associations of birth weight and infant growth with physical fitness. This secondary aim of the study is also described in this chapter. Because of the pivotal role of ANS in cardiovascular disease, we focused on ANS activity as a potential underlying mechanism in the DOHaD concept in **Chapter 8**. In this chapter we describe the relation of birth weight and infant growth with childhood ANS activity in the ABCD cohort and we assess the potential mediating role of ANS activity in the association of early growth with energy balance-related behaviors.

We conclude this thesis by reflecting on the main findings of this thesis, discussing the broader perspective of our results, their clinical and methodological limitations and the implications for public health policies in **Chapter 9**. In addition, we propose directions for future research on the Developmental Origins of Energy Balance-Related Behavior and Physical Fitness in this chapter.

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3. STUDY PROTOCOL:

THE ASSOCIATION OF BIRTH WEIGHT AND INFANT GROWTH TRAJECTORIES WITH PHYSICAL FITNESS, PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR AT 8-9 YEARS OF AGE

THE ABCD STUDY

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Based on BMC Pediatr. 2013 Jul 9;13:102.

ABSTRACT

BACKGROUND. Low birth weight and accelerated infant growth have been identified as independent risk factors for childhood and adult obesity and cardiovascular disease. This led to the 'Developmental Origins of Health and Disease' (DOHaD) hypothesis, stating that environmental factors during pregnancy and early postnatal life affect disease risk in later life. There is growing evidence that perinatal factors may influence adult health through the programming of energy balance regulation, including sedentary behavior and physical activity. The present study focuses on the influence of birth weight and infant growth on physical fitness, physical activity and sedentary behavior in 8-9 year old children, as this might partly explain the higher obesity and cardiovascular risk associated with low birth weight and accelerated infant growth. In addition, this study provides the opportunity for a validation study of a linguistic and cross-cultural translated physical activity questionnaire compared to accelerometer data. This article describes the study protocol for this study.

DESIGN. This is a study embedded in the Amsterdam Born Children and their Development (ABCD) birth cohort. In 200 children of Dutch ethnicity, physical fitness, physical activity and sedentary were assessed at age 8-9. We measured aerobic fitness using the 20-meter multistage-shuttle run-test, and neuromuscular fitness using the standing broad jump and handgrip strength test. Sedentary behavior and physical activity levels were measured using accelerometry. All children also completed a translated physical activity questionnaire, the scores of which will be compared to accelerometry data to assess the construct validity of the questionnaire in Dutch school-aged children.

DISCUSSION. This study will be the first population-based prospective cohort study to address the association of both prenatal and postnatal growth with physical fitness and objectively-assessed physical activity and sedentary behavior. This will contribute to a better understanding of the way perinatal growth relate to lifestyle and obesity in later life. The results may guide both future studies in the field of DOHaD, and public health strategies in the prevention of childhood obesity.

BACKGROUND

In the 1980s Barker and Hall reported a series of studies regarding the association between low birth weight and death from coronary heart disease, suggesting that prenatal environmental factors are involved in the aetiology of adult-onset diseases.[1, 2] In the following decades numerous epidemiological studies substantiated a close association between low birth weight and an increased risk of developing adult diseases, including cardiovascular disease[3, 4], stroke[5], type 2 diabetes mellitus[6], hypertension[7], adiposity[8], osteoporosis[9], polycystic ovarian syndrome[10], depressive disorders[11], and psychoses.[12] These observations led to the 'Developmental Origins of Health and Disease' (DOHaD) hypothesis.[13] This hypothesis proposes that the fetus adapts to a substrate-limited intrauterine environment with so called predictive adaptive responses, resulting in permanent changes in tissue differentiation and hormonal and metabolic set points. In this way programming results in irreversible adaptations which enhance survival during postnatal nutritional constraint, but may increase susceptibility to adult-onset diseases in a substrate-rich environment after birth.

As the number of DOHaD related studies grew, several important additions and refinements to the hypothesis were made. First, an important feature of the epidemiological observations is that adult disease risk is continuous within the normal range of birth weight, rather than being a pathological feature which is expressed below a critical cut-off point.[14] Second, in addition to the role of the intrauterine environment, more recent observations have also drawn attention to the significance of infant growth in the predisposition to adult disease. Accelerated growth in infancy increases risk of obesity[15], type 2 diabetes[16], hypertension[17] and cardiovascular disease.[18] Thus, the critical window for developmental responses may extend into early postnatal life. Last, subtle sex differences in the progression and development of adult diseases are observed, with female offspring being relatively protected from the adverse effects of perinatal malnutrition.[19, 20] The cause of this sex difference remains unclear, but a protective effect of female sex hormones is proposed as an intriguing mechanistic explanation.

Obesity plays a critical role in the association between perinatal growth and adult disease, often preceding insulin resistance, dyslipidemia, and hypertension in children and young adults.[21] Given that obesity is fundamentally the result of an inadequate energy balance regulation, in which energy intake exceeds expenditure, its developmental origins cannot be explained by structural changes or neuroendocrine dysregulation alone.[22] Therefore, research on the pathogenesis of obesity has recently focused on the developmental origins of behavior that is closely related to energy expenditure and energy intake, i.e., feeding behavior, physical activity and sedentary behavior.

Physical activity (PA) and sedentary behavior are components of energy expenditure that vary considerably between persons as well as for a given person over time.[23, 24] Sedentary behavior refers to activities that involve little energy expenditure, such as lying down, sitting, watching television, using the computer and other forms of screen based entertainment.[25] Sedentary behavior is thereby a distinct class of behaviors rather than being the absence of PA.

Both PA and sedentary behavior are of particular interest in the study of the Developmental Origins of energy balance regulation. Animal studies have shown that offspring of nutritionally impaired pregnancies are significantly less physically active than controls, and show increased sedentary behavior.[26-28] These effects on PA and sedentary behavior seem to originate from programming of the hypothalamic pathways which regulate energy homeostasis.[29] In humans, several clinical studies also identified low birth weight as a predictor for lower PA levels and more sedentary behavior in children and adults[30-34], although others failed to confirm this relationship[35-41], and there are suggestions that the association may be limited to very low birth weight individuals.[32]

Physical fitness is generally defined as the ability to perform sports or occupations, and is bidirectionally related to PA.[42] As recent data indicates, regular PA improves physical fitness, and conversely, a high level of physical fitness promotes higher PA levels.[43] It is therefore apparent that unfit children are less inclined to be physically active, which has considerable potential to increase later disease risk. There are many dimensions to fitness, of which aerobic fitness (also known as cardiorespiratory endurance) and muscular strength are most consistently associated with physical performance and cardiovascular health.[44-46] Although fitness can be improved by regular PA, it is partly genetically determined, and perinatal influences may attenuate or strengthen this predetermined fitness level.[47] Indeed, several studies consistently found lower muscle mass and strength in lower birth weight adults and children.[48] For aerobic fitness, the findings are less robust. A number of studies found a significant positive association between birth weight and aerobic fitness in childhood and adulthood[34, 49, 50], but others did not.[51, 52] Differences in subject age, sample size, type of fitness test used and severity of growth retardation in the cohort may explain these contradictory reports.

The current evidence suggests that physical fitness and PA may have a combined and accumulative effect on cardiometabolic health from an early age. Especially body fatness is inversely associated with fitness and PA levels.[42] But improved physical fitness and PA also promote a healthier cardiovascular risk profile in children independently from body fatness, including lower blood pressure, higher HDL cholesterol, lower triglycerides, improved glucose tolerance and post-prandial lipidemia, and modified clotting factors.[42, 53]

Therefore, variations in physical fitness and PA might impact future health of children irrespective of obesity risk.

In recent years, sedentary behavior has been identified as a distinct health risk factor. For example, sedentary behavior has been shown to be positively associated with an increased risk of type 2 diabetes, cancer, and all-cause and CVD mortality in adults.[54-56] These associations are shown to be at least partially independent of levels of PA. Reviews of the relationship between sedentary behaviors and obesity in children and adolescents found a positive association, suggesting that sedentary behavior is a risk factor for the development of obesity in children.[57, 58] Another review, however, concluded there was insufficient evidence for a longitudinal relationship between childhood sedentary time and cardiovascular health indicators, because of a lack of high quality studies addressing this topic.[59]

Based on the aforementioned data, we hypothesize that low birth weight and accelerated infant growth is associated with lower levels of aerobic fitness, muscular strength and PA and more time spent on sedentary behavior in school aged children, contributing to the increased propensity to obesity and related diseases in later life. The hypothesized model is shown graphically in figure 3.1.

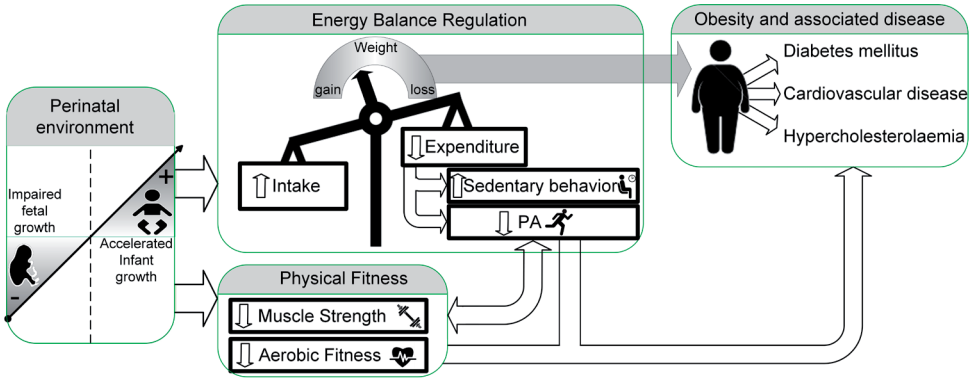

Figure 3.1 Graphical representation of the hypothesized associations of the perinatal environment with obesity and associated diseases through physical fitness, physical activity and sedentary behavior Abbreviations: PA – Physical activity.

This paper describes the rationale and design of a study aiming to examine the association of birth weight and infant growth trajectories with aerobic fitness, muscular strength and objectively assessed sedentary behavior and PA levels in 8-9 year old children. In order

to assess whether an accurate assessment of regular PA can be obtained by self-report questionnaires in Dutch children, we will additionally validate a linguistic and cross-cultural translation of a commonly used PA questionnaire in 8-9 year old children. If validity of this questionnaire has been confirmed in our subgroup, we may use it to assess PA and sedentary behavior of our entire cohort in a future phase of the ABCD study. This article outlines the development of this PA questionnaire.

STUDY OBJECTIVES

The primary study objectives are to examine the association of birth weight and infant growth trajectories with (i) aerobic fitness assessed by the 20 meter multistage shuttle run test (20-m MSRT), (ii) muscular strength assessed by the standing broad jump (SBJ) and hand grip strength test, and (iii) physical activity levels and sedentary time assessed by accelerometry, at 8 to 9 years of age. We will control for potential confounders, such as maternal factors (e.g., maternal age, pre-pregnancy body-mass index (BMI), maternal height, socio-economic status) and child factors (e.g., gender, age, height, BMI, gestational age, Apgar score), and test for possible effect modification by gender. (see Table 3.1) A secondary objective is to examine the construct validity of a self-report extensive PA questionnaire, based on the internationally employed Physical Activity Questionnaire for Older Children (PAQ-C) and Children's Leisure Activities Study Survey (CLASS). This PA questionnaire is provided in the supplementary file 3.1.

Table 3.1 Overview of study variables

Study Outcome			Determinants		Potential confounders
Construct	**Component**	**Test(s) (unit)**	**Construct**	**Variable(s) (unit)**	**Variable(s) (unit)**
Physical Fitness	Aerobic fitness	20 meter multistage shuttle run test (stage)	Intra-uterine growth	Birth weight (SD)	*Subject-specific:* Gender (male/female) Age (years) Height (cm) BMI (kg/m^2) Gestational age (days) Apgar score (score at 5 min)
	Muscular strength	Hand grip strength test (kg) Standing Broad Jump test (cm)	Infant growth	Average standardized growth velocity 0-12 months (ΔSDS)	*Family-specific*: Maternal age (years), Maternal height (cm) pre-pregnancy BMI (kg/m^2), socio-economic status (class)
Physical activity	Moderate to vigorous physical activity	Accelerometry (minutes/day) PA questionnaire (score)			
Sedentary behavior	Sedentary time	Accelerometry (minutes/day) PA questionnaire (score)			

Table 3.1 Overview of the primary study outcomes (left column) and determinants (middle column). Described are the studied constructs with the corresponding tests and units of measurement. The right column displays the potential confounders we will control for. Abbreviations: kg – kilogram;, cm – centimeters; SD – Standard Deviations; ΔSDS – difference in Standard Deviation Scores.

METHODS AND DESIGN

Setting

This study is embedded in the Amsterdam Born Children and their Development (ABCD) study, a prospective birth cohort study aimed at the identification of prenatal and early life influences on health at birth and in later life. The project is carried out by a multidisciplinary team of researchers from the Public Health Service Amsterdam, the Academic Medical Center and VU University Medical Center.

The design and conceptual framework of the overall ABCD study has been previously described in detail.[60] In summary and relevant to the current study, the ABCD study included 8266 women pregnant between January 2003 and March 2004. These woman completed questionnaires during and after their pregnancies, covering sociodemographic data, lifestyle, dietary habits and psychosocial factors, conventional medical and obstetric history, and perinatal details. Birth weight of the children was obtained from the Child Health Care Registration, the office that also performs neonatal blood screening for inborn errors of metabolism, as is routinely performed in the Netherlands in the 1st week of life. Until the age of 4 years, height and weight measures of these children were routinely collected as part of regular preventive Child Health Care. These measurements took place during on average 14 regular follow-up moments and were performed by qualified nurses and physicians. Of the 6735 women who gave permission for follow-up of their child, 6575 mothers also consented to follow up of their child's growth data.

In 2008, around their 5th birthday, 3321 children completed a 'health check'. At the appointment for this health check we collected data on anthropometrics, blood pressure, heart rate variability, body composition and a capillary blood sample to determine lipid profile, glucose, insulin, C-peptide, HbA1c and albumin. In addition, parents completed questionnaires about the child's health, development and behavior, family socio-demographics, maternal lifestyle and psychosocial conditions and family history of medical conditions.

Birth weight and infant growth

The primary determinants in our study are birth weight and infant growth trajectories. Birth weight is hereby used as a surrogate marker for intrauterine growth, and an established index for the intrauterine environment.

Birth weight is expressed as standard deviation (SD) score, adjusted for gestational age, maternal height, weight, parity, ethnicity and fetal sex, in accordance with the recommendations of Gardosi.[61] Low birth weight is defined as a birth weight below

the 10th percentile (-1.28 SD). Infant growth is expressed as the average standardized growth velocity, defined as the change in SD score between birth and 12 months. We will examine growth in weight-for-age, height-for-age and weight-for-height. We expect the association with the outcome measures to differ for each expression of growth, with the strongest association for weight-for-age. Accelerated growth is defined as >0.67 change in SD score. This 0.67 SD represents the distance between two adjacent growth lines on standard infant and childhood growth charts (i.e., the 2nd, 10th, 25th, 50th, 75th, 90th and 98th centile lines). The adopted definitions of low birth weight and accelerated infant growth are based on recommendations of Monteiro *et al*.[15], and in line with recent other studies addressing the DOHaD hypothesis.[62-65]

Current study population

The current study is conducted in a subgroup of the ABCD birth cohort. At the time of the data collection, the children were 8 or 9 years of age. Children were eligible for this study if (i) they fully completed the ABCD age 5 health check and (ii) were of Dutch ethnicity (i.e. with both parents born in the Netherlands). This is to exclude confounding by ethnicity. Exclusion criteria were (i) a personal history of neurological, cardiovascular or metabolic disease, (ii) any musculoskeletal injury or disability or (iii) the use of any medication at the time of data collection.

Sample size calculation

Based on the literature, we expected to find a difference between low birth weight and normal birth weight children of one stage on the 20-m MSRT, with a standard deviation (SD) of two stages[49, 66], and a difference of 10 cm on the SBJ test, with a SD of 25 cm.[67] A similar difference in 20-m MSRT and SBJ test scores between children with normal and accelerated infant growth was anticipated, but as there is no literature on this topic available, a scientific basis for this assumption is lacking. With a significance level of 5% and a power of 80% in total 100 children per group were required.

Recruitment

To ensure an adequate number of children in each subgroup, we selected more children with low birth weight than that would be selected by random sampling. This to ensure power of the study that may be lost in a more generalized sampling technique.

A recruitment letter, explaining study objective and design in detail, was sent to all children´s parents. For the children, simplified written information was provided. Informed and written consent were obtained from parents before participation. The Amsterdam Medical Center's Ethics Committee approved the study protocol, and all procedures were

performed in accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 2008.[68]

Study design

Three identical measurement periods were arranged two or three weeks apart. Each measurement period consisted of (A) the self-completion of a PA questionnaire, (B) a physical fitness test battery, and (C) wearing an accelerometer for seven consecutive days.

A. Modified physical activity questionnaire

After written consent was obtained, a PA questionnaire was sent to the children by surface mail. The questionnaire was completed at home and handed back at the day of the physical fitness test battery. Responses were checked for completeness by staff.

The PA questionnaire is a cross-cultural adaptation of the Physical Activity Questionnaire for Older Children (PAQ-C)[69] and the Children's Leisure Activities Study Survey (CLASS) [70]: two standardized activity questionnaires for children, both of which recall activities over the previous seven days.

The PAQ-C is a 7-day self-reported recall instrument, developed to assess general levels of PA throughout the elementary school year for children approximately 8 to 14 years of age.[71] It provides a summary PA score derived from nine items. Each question is scored on a 5-point scale, with higher scores indicating higher levels of activity. The first question is a checklist of 22 common leisure and sports activities. Because the PAQ-C only assesses the frequency of activities, we added elements of the CLASS addressing duration of the activities. For each PA in the checklist, children were asked to report the frequency and duration spent in that activity. The next six items addresses PA during physical education classes, recess, lunch break, right after school, in the evenings, and on the weekend. Item eight asks which statement "describes you best for the last seven days" with five statements describing low to very high activity levels. The ninth item asks the child how often he/she participated in PA on each day of the week.[69]

The PAQ-C is widely accepted[72-74] and recommended[75] for international and national studies. In addition, a systematic review of measurement properties of self-report PA questionnaires for children concluded good to moderate validity and reliability of the PAQ-C.[76] The CLASS questionnaire was found to have weak to moderate validity and reliability. Nonetheless, both the PAQ-C and CLASS questionnaire were considered amongst the most promising PA questionnaire for children.[76]

Translation of the physical activity questionnaires

The aim of the translation process was to develop a Dutch version of the PAQ-C that is conceptually equivalent but adapted to represent common Dutch physical activities. The translation process was carried out using a forward-backward translation technique.[77-79] First, three researchers, native Dutch speakers and fluent in English, produced independent forward translations of the original PAQ-C and CLASS questionnaire. Then, the researchers and the project manager produced a reconciled Dutch version based on the forward translations and the original questionnaires, and an English report documenting the synthesis process, the issues addressed, and how they were resolved. Then, a native English and fluently Dutch speaking translator, who was blind to the original version, translated this reconciled Dutch version back into English. One of the researchers and the project manager compared the back-translated version with the original version, assessing inaccuracies, misunderstandings or mistranslations, and produced a prefinal version. The project manager and all involved researchers replaced PA items that are rarely conducted by Dutch children (e.g., Australian football, cross-country skiing) by items that are more commonly practiced (e.g., playing tennis, badminton, practicing judo). This version was administered to ten Dutch children of primary school age (i.e., the target population) checking the comprehensibility of each item. As there were no ambiguities reported, we concluded that the adapted version retained its equivalence in an applied situation. The final PA questionnaire used in this study is provided in the supplementary file 3.1.

B. Physical fitness test battery

A physical fitness test battery was developed using the evidence-based recommendations of the ALPHA health-related fitness test battery for children and adolescents[80] and the Eurofit Fitness test Battery.[81] We successively assessed anthropometry, blood pressure, maximum muscle strength, explosive muscle strength and aerobic fitness.

Anthropometry

Height and weight were measured with the children dressed in light sportswear. Height was measured to the nearest millimetre using a Leicester portable height measure (Seca), and weight to the nearest 100 gram using a Marsden weighing scale, model MS-4102.

Blood pressure

Blood pressure was measured two times on the right arm in a sitting position after a few minutes rest. If the difference between the measurements was more than 10mmHg for either systolic or diastolic pressure, a third measurement was obtained. The device used was the Omron 705 IT (Omron Healthcare Inc, Bannockburn, IL, USA) with an appropriate sized cuff. Outcome measures were systolic pressure (SP), diastolic pressure (DP), and

mean arterial pressure (MAP), all expressed in mmHg. MAP was calculated using the following equation: MAP = DP + 1/3 (SP-DP).[82]

Muscular strength

With the standing broad jump (SBJ) and hand grip strength test we assessed explosive muscle strength and maximum muscle strength, respectively.

In the SBJ test, the child attempts to jump as far as possible with feet together. From a starting position immediately behind a line with feet slightly apart, the child jumps using both feet with take-off and landing, swinging the arms and bending the knees to provide forward drive. The distance was measured from the take-off line to the point where the back of the heel nearest to the take-off line lands, and reported in centimeters. The test was repeated twice, and the best score retained.

Hand grip strength was measured using a hand dynamometer, with the scores recorded in kilograms (kg). The reported precision is 0.5 kg. The test was performed twice (alternately with both hands), with the dynamometer adjusted to the age- and gender-specific optimal grip span, as this seems the most appropriate protocol to evaluate maximal hand grip strength in children.[83]

The SBJ test seems to be the most valid test assessing lower body muscular strength compared to other muscular strength tests (i.e., bent and extended arm hang, squat jump, countermovement jump, Abalakov jump), showing the highest associations with isokinetic parameters.[80] In addition, Castro-Piñero *et al*. concluded that the SBJ test can be considered a general index of lower body muscular fitness in children, based on a strong association with other lower body muscular strength tests (R^2 = 0.83–0.86), as well as with upper body muscular strength tests (R^2 = 0.7-0.9).[67] Milliken *et al*. analyzed the association between hand grip strength and chest press in children aged 7-12 years and found that the hand grip strength test is valid to assess upper body maximal strength (R^2 = 0.70).[84]

Aerobic fitness

We measured aerobic fitness using the 20 meter multistage shuttle run test (20-m MSRT); a simple non-invasive, valid and reliable field test providing an estimate of maximal cardiorespiratory capacity.[85] The test was conducted as described by Léger *et al*.[86] On an outdoor field, children were required to run between two lines 20 meter apart, while keeping pace with beeps emitted from a pre-recorded CD. The initial speed was set at 8.5 $km \times h^{-1}$ (2.4 $m \times s^{-1}$), increasing by 0.5 $km \times h^{-1}$ (0.1 $m \times s^{-1}$) with each stage thereafter (one stage takes one minute). Children were instructed to run in a straight line, to pivot and

turn on completing a shuttle, and to pace themselves in accordance with the beeps. The test ended when the child failed to reach the end line concurrent with the beeps on two consecutive occasions. The children were verbally encouraged by the researchers to run for as long as possible throughout the course of the test. The last completed half-stage of the 20-m MSRT was recorded and used as a valid proxy for aerobic fitness.[87, 88]

The 20-m MSRT has several advantages over other field tests, such as tests that cover as much distance as possible in a set time[89], or tests that cover a set distance in the fastest time possible.[90] First, the 20-m MSRT has a graded physiological response and the absence of individual pace control.[91, 92] Second, it can be administered in a relatively small space and is therefore easy to implement without extensive facilities. Third, children are known for their frequent stops, starts, and turns in their daily PA. Therefore, it may be a more relevant test than a continuous directional run.

C. Accelerometry

Accelerometers have shown to provide reliable estimates of overall PA, sedentary behavior and PA-related energy expenditure among children.[93, 94] In this study, PA and sedentary behavior were objectively assessed using two models of Actigraph (ActiGraph, LLC, Fort Walton Beach, FL) accelerometers, namely triaxial Actitrainers (dimensions: 8.6 cm × 3.3 cm × 1.5 cm, weight: 51 grams) and GT3Xs (dimensions: 3.8 cm × 3.7 cm × 1.8 cm, weight: 27 grams). These are omnidirectional accelerometers, sensitive to movement in all directions.

Researchers distributed the accelerometers face-to-face at the end of the physical fitness test battery. Information about accelerometer use was given to the children and parents orally. Researchers placed the accelerometer to the children's waist using an elastic waistband, and they told the children not to remove the device for seven days except during sleeping, swimming and bathing. Additionally, children and parents received a brochure with information about accelerometer use and a compliance log. Children had to self-complete this compliance log for the duration of the accelerometer data collection, as this is an effective, low cost method to increase compliance.[95] Each day, the children recorded the time they got up and went to bed, whether or not it was a school day, and whether the accelerometer was removed during the day, and if so, for what reason. After the proposed wearing period, the devices were collected at the child's home by the researchers. Downloading the data from accelerometers was done as soon as possible on the same computer where it was initialized to prevent disturbances that can be caused by the time offset between computers.[96]

The accelerometer signal is summarized over a user-defined period of time, called epoch, into what are called counts. The higher the number of counts, the higher the intensity of PA. As children tend to have short bursts of PA[97], we selected an epoch length of 15 seconds to accurately capture this spasmodic PA pattern.[98] Non-wearing time was defined as more than 20 minutes of consecutive zero counts. Wearing time was calculated by subtracting non-wearing time from 24 hours. To capture a representative portion of daily PA, only days with at least 10 hours of wearing time were considered valid.[99] Children who had at least three valid weekdays and one valid weekend day were included in further data analysis.[100] Based on the cut-off values of Treuth *et al*. we defined minutes spent in sedentary, light, moderate and vigorous activity, as <100, 100 – 2999, 3000 – 5199 and ≥5200 counts per minute (c.p.m.), respectively.[101]

Statistical Analysis

Data will be presented as means ± SD for continuous variables, and as percentages for categorical variables.

For every primary outcome, its association with standardized birth weight and infant growth will be assessed using multivariable linear regression analysis. First, birth weights and infant growth trajectories will be dichotomized as normal vs. low birth weight and normal vs. accelerated infant growth, respectively, and analyzed together in a linear regression analysis to account for mutual interference. To assess whether the effect of low birth weight and accelerated infant growth exceeds the sum of each exposure separately, we will subsequently add an interaction term of birth weight with infant growth to the model. A p-value less than 0.10 for the interaction term is considered indicative of effect modification, after which a subgroup analysis will be performed with the children divided into four subgroups (normal birth weight and normal infant growth; low birth weight and normal infant growth; normal birth weight and accelerated infant growth; low birth weight and accelerated infant growth).

A scatterplot will be employed to identify potential linear associations of either birth weight or infant growth with the outcome variable. If the scatterplot suggests a linear association of either birth weight or infant growth with the outcome, we will additionally run the analysis with the respective dichotomized variable replaced by its continuous equivalent.

The model will be adjusted for potential confounding, by addition of the potential confounders group-wise in a multivariable linear regression analysis. The first group of potential confounders are subject-specific variables (gender, current age, height, BMI, gestational age, Apgar score), the second are family-specific variables (socio-economic

status (defined as maternal level of education), maternal age, maternal height, maternal pre-pregnancy BMI). Effect modification by gender will be evaluated by addition of an interaction term of gender with either birth weight or infant growth.

Validity assessment of the questionnaire

To assess the construct validity of the modified PA questionnaire, PAQ-C summary scores will be examined as originally constructed (the average of the nine questions).[69] Pearson's correlation coefficient between the PAQ-C summary score and accelerometer-assessed moderate to vigorous PA (MVPA) will be calculated, to assess the construct validity of the PA questionnaire compared to accelerometry. In addition, the common leisure and sports activities assessed in the first question are assigned metabolic equivalent units (METs) based on the MET values given in the recently updated 2011 Compendium of Physical Activities.[102] These activities are classified as sedentary (<2 MET), light (2-4.5 MET), moderate (4.6-6.5 MET) or vigorous (more than 6.5 MET) PA, and grouped together to assess the daily time spent in each PA level. Agreement between self-reported minutes in MVPA and minutes in MVPA according to accelerometry data will be examined using the Bland–Altman procedure.[103] A similar approach will be used to assess the agreement between self-reported and accelerometry assessed sedentary time. The Bland-Altman procedure plots the differences between the self-reported and accelerometry data against their mean, where ±1.96 SD of the differences provides an interval within which 95% of the differences between the two sets of measurements are predicted to fall. A higher level of agreement is illustrated by a mean difference closer to zero and a smaller range of the 95% confidence interval.

DISCUSSION

Although low birth weight and accelerated infant growth have been consistently linked to childhood and adult obesity[8, 15], the underlying disturbances in energy balance regulation still remain poorly understood. The present study focuses on the developmental origins of physical fitness, physical activity and sedentary behavior in 8-9 year old children, as this might partly explain the higher obesity and cardiovascular risk associated with low birth weight and accelerated infant growth. In addition, this study provides the opportunity for a validation study of a linguistic and cross-cultural translated PAQ-C and CLASS questionnaire compared to accelerometer data. If the validation study suggests that the translated questionnaire is a valid tool to assess PA and sedentary behavior in this subgroup, it may be used in a later stage of the ABCD study, to assess PA and sedentary behavior in our entire birth cohort.

To our knowledge, this study is the first prospective cohort study addressing the association of both birth weight and infant growth with objectively assessed PA and sedentary behavior, aerobic fitness and muscular strength in later childhood. A major strength of this study is that it is conducted within the framework of the ABCD study, a prospective cohort study with extensive data on birth outcome, growth patterns, and lifestyle factors, amongst others. This provides the opportunity to control for a broad range of potential confounders, like BMI, gestational age, Apgar score, maternal age, maternal pre-pregnancy BMI, and socio-economic status. All these variables are prospectively collected and assessed during the course of the ABCD study.[60]

A limitation of this study is that only children of Dutch ethnicity are included, to exclude confounding by ethnicity. As there are known ethnic differences in both obesity risk[104, 105] and PA levels and sedentary behavior[106, 107], the results might not be applicable to other ethnic groups. In addition, selective nonresponse in this study may lead to an oversampling of physically fit children, as these children might be more willing to participate in a study on PA and fitness. Both these aspects hamper the generalizability of the results.

In this study design, and in many others, birth weight below the 10th percentile is used to identify intrauterine growth retardation.[108] However, this is only a very crude indicator[109], and there is increasing evidence that insults during fetal life can have long-term consequences independently of birth weight.[110] On the other hand, a low birth weight subject could be small at birth because of genetic reasons or maternal characteristics, and indeed have had a perfectly well-nourished fetal life. The use of customized growth standards to identify low birth weight subjects, in line with Gardosi's recommendations[61], may partly avoid misclassification. Nonetheless, instead of a 'present' or 'absent' definition of low birth weight, it is considered more informative to assess whether there is a continuous association of outcome with birth weight.[110] In fact, substantial epidemiological data indicate there is a continuous inverse association of birth weight with certain chronic diseases.[7, 9, 111] In line with this, if we find a linear association of birth weight and/or infant growth with the outcome measure, we will report the results of linear regression analyses with birth weight both dichotomized as well as a continuous variable.

While the significance of infant growth in the predisposition to adult disease has extensive support from observational studies, it is not clear whether the detrimental adult outcomes (obesity and cardiovascular disease) are related to a specific time window. Different studies vary widely in definition and duration of accelerated growth, with the period of growth evaluated being as short as 1 week[112] up to the first 7 years of life.[18] A consistent age

interval used in several studies was 0-1 year and 0-2 years, all of which also used the +0.67 weight-for-age SD score variation cut-off point as a definition for accelerated growth.[15] In line with the recommendations[15] and recent other studies[62-65], we will adopt the 0-1 year age interval and the 0.67 SD score variation for the period of infant growth and the definition of rapid growth, respectively.

There are consistent relations between PA and fitness status in adults and children.[42] Physical fitness is in part determined by PA patterns over recent weeks or months, although the improvement in fitness to a standard exercise dose varies widely and is considered predisposed.[113] It is stated that such individual predisposition reflects genetic traits[47], but the programming of PA patterns based on early life experiences offers an alternative explanation. Conversely, higher levels of physical fitness, especially aerobic fitness, may promote higher PA levels. As sports and active play may be more easy, successful and rewarding for the physically fit, these children may engage in PA more often. This poses individuals at the lower end of the activity and fitness distribution at considerable risk of a downward spiral of inactivity leading to reduced fitness and reduced fitness leading to less activity. Given the strong and consistent inverse relations of physical fitness and PA with obesity and cardiovascular risk profile, this will have detrimental effects on later health.[42, 53]

If the present study indeed shows that physical fitness, PA and sedentary behavior are significantly associated with birth weight and infant growth, further assessment of the potential mechanisms underlying these associations is required. For example, animal studies provide evidence that sympathetic nervous system (SNS) function is likely to be involved in the developmental origins of later obesity risk. Perinatal insults have been reported to alter SNS development, which may persist throughout life.[114] In human studies, an inverse association between birth weight and SNS activity in middle-aged adults[115], young adults[116] and adolescents[117] was found, although a study in neonates born small for gestational age found no such association.[118] SNS hyperactivity may contribute to obesity through increased food intake[119], altered glucose metabolism[120], and decreased energy expenditure.[121] Whether these developmentally-induced variations in SNS function influence PA and fitness remains to be investigated. In addition, alterations in body composition are widely believed to contribute to the pathogenesis of obesity and its complications. Low birth weight has been linked to lower adult and childhood muscle mass[48] and altered muscle metabolism.[122] To what extent these developmental influences on skeletal muscle mass and function explain variations in physical fitness and activity needs further investigation.

In conclusion, this study examines developmentally-induced variations in physical fitness, PA and sedentary behavior in children aged 8-9 years and contributes to an improved understanding of the perinatal influences on energy balance regulation. This knowledge may guide future studies in the field of developmental origins of obesity and related diseases. In addition, the results might initiate preventive public health strategies, as the early promotion of an active lifestyle may be an effective and efficient way to attenuate later disease risk in low birth weight and infant growth accelerated children.

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4. THE ASSOCIATION OF BIRTH WEIGHT AND INFANT GROWTH WITH ENERGY BALANCE-RELATED BEHAVIOR

A SYSTEMATIC REVIEW AND BEST-EVIDENCE SYNTHESIS OF HUMAN STUDIES

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Based on PLoS One. 2017 Jan 12;12(1):e0168186

ABSTRACT

BACKGROUND. Suboptimal prenatal and early postnatal growths are associated with obesity in later life, but the underlying mechanisms are unknown. The aim of this study was to systematically review the literature that reports on the longitudinal association of (i) birth size or (ii) infant growth with later (i) energy intake, (ii) eating behaviors, (iii) physical activity or (iv) sedentary behavior in humans.

METHODS. A comprehensive search of MEDLINE, EMBASE, PsycINFO and The Cochrane Library was conducted to identify relevant publications. We appraised the methodological quality of the studies and synthesized the extracted data through a best-evidence synthesis.

RESULTS. Data from 41 publications were included. The quality of the studies was high in three papers, moderate in 11 and low in the large majority (n=27) of papers appraised. Our best-evidence synthesis indicates that there is no evidence for an association of birth weight with later energy intake, eating behavior, physical activity or sedentary behavior. We found moderate evidence for an association of extreme birth weights (at both ends of the spectrum) with lower physical activity levels at a later age. Evidence for the association of infant growth with energy balance-related behavior was generally insufficient.

CONCLUSIONS. We conclude that current evidence does not support an association of early-life growth with energy balance-related behaviors in later life, except for an association of extreme birth weights with later physical activity.

INTRODUCTION

There is now an abundance of literature highlighting the importance of early life growth on adult-onset disease risk. Low birth weight, as a marker of suboptimal prenatal growth, is strongly linked to central obesity[1], cardiovascular disease[2] and type 2 diabetes.[3] In addition to low birth weight, high birth weight and accelerated postnatal weight gain have also been independently associated with cardiometabolic disease and obesity.[4] These associations may reflect physiological predictive adaptive responses to early life environmental cues, with long-term structural and/or functional changes that influence later health and disease risk.[5]

One of the hypothesized mechanisms underlying the association of pre- and early postnatal growth with later obesity and cardiovascular disease is the alteration of energy balance-related behaviors, including eating behavior, physical activity (PA) and sedentary behavior (SB). Several studies in rodents have shown that impaired prenatal nutrition followed by increased postnatal growth causes excessive intake and diminished PA in the offspring, preceding the development of obesity.[6-8] The hypothesis that early growth affects long-term energy balance regulation seems plausible as the hypothalamic neuro-endocrine circuits involved in energy homeostasis are highly sensitive for nutritional influences during gestation and directly after birth.[9] However, caution is needed when extrapolating findings from these rat studies to the human situation, because the timing in the development of energy-balance regulation is different between species and because the nutritional regimens used to model early life malnutrition are rather extreme, with intakes reduced to 30% of controls.[8] This might induce a pathological response not directly relevant to the normal human pregnancy.

Human data on the association of pre- and early postnatal growth with energy balance-related behaviors are limited and show conflicting results. For example, some studies found a positive association of birth weight with PA[10], whereas others reported no associations[11], inverse associations[12], PA-specific associations[13], age-specific associations[14] or gender-specific associations.[15] Factors that may contribute to the equivocal association of perinatal growth with energy balance-related behavior include differences in study population, the severity of growth retardation in low birth weight subjects, methodology pertaining to data collection (such as use of questionnaires) and different types of PA studied.

Reviews have summarized the association of pre- and early postnatal growth with either energy intake[16-18], or the combination of energy intake with PA[19-21]. The majority of reviews concluded that suboptimal pre- and early postnatal growth has negative effects

on these behaviors in later life. However, these conclusions are mostly based on a non-systematic search of the literature, with evidence derived from animal models and the studies' quality not taken into account. Øglund *et al.* reviewed the literature on the relation of perinatal growth with accelerometer-assessed PA in children and concluded that there is no evidence for an association of birth weight with childhood PA based on a formal meta-analysis.[22] However, the authors could only include five of nine identified studies in their meta-analysis because of the heterogeneity of the reported data. In addition, the methodological quality of the studies was not accounted for. A best-evidence synthesis overcomes these limitations by synthesizing all the available evidence and weighing the methodological quality of the studies.

In the present systematic review we assess the association of birth weight and infant growth with energy balance-related behaviors in children, adolescents and adults, including a quality assessment and data synthesis of evidence from human studies on the association of (i) birth size and/or (ii) infant growth with later (i) energy intake, (ii) eating behavior, (iii) PA levels and/or (iv) SB.

METHODS

Literature search

A comprehensive systematic search was performed in the bibliographic databases PubMed, EMBASE.com, PsycINFO (via EBSCO) and The Cochrane Library (via Wiley) from inception to January 5th, 2016. Search terms included controlled terms from MeSH in PubMed and EMtree in EMBASE.com, thesaurus terms in PsycINFO as well as free text terms. In The Cochrane library only free text terms were applied. Search terms expressing perinatal growth (e.g., birth weight, infant growth, etc.) were used in AND-combination with terms representing 'Energy balance-related behaviors' (e.g., sedentary, intake, activity, etc.). If possible, the search was restricted by excluding non-relevant publication types (e.g., editorials, practice guidelines, biographies, etc.). The full search strategy is available as online supplement on the journal's website. Additionally, the reference lists of all selected articles and published reviews on this topic were screened for potentially relevant publications (backward citation tracking), and we used Science Citation Index to identify all the subsequent articles that cite any of the selected articles or relevant reviews (forward citation tracking).

Eligibility criteria

Studies were included if they met the following criteria: (i) the study was a (historical or birth) cohort study; (ii) the study described at least one anthropometric measurement

during birth or change in anthropometric measurements in infancy; and (iii) the dependent variable was a measure of energy intake, eating behavior, PA or SB. We excluded: (i) animal studies; (ii) studies reporting on the effects of an (nutritional) intervention or famine exposure; (iii) publications written in another language than English, German, French or Dutch; (iv) certain publication types: editorials, legal cases, interviews, etc.

Definition of the outcome variables

The following definitions were used to help guide the eligibility assessment: energy intake is the amount of energy consumed as food (expressed in calories or joules) per unit of time (mostly day); eating behavior is the patterns of behaviors (thoughts, actions and intents) that a person enacts in order to regulate its energy intake[23]; PA is any bodily movement produced by skeletal muscles that requires energy expenditure, such as active transportation or participation in sports[24]; and SB refers to any waking activity characterized by an energy expenditure ≤ 1.5 metabolic equivalents and a sitting or reclining posture, such as sitting, watching TV, playing video games.[25] Eligible outcome measures included those obtained by objective measures (e.g., weighing of foods, observation of behaviors, or activity measurements by accelerometer) and self-/parent-reports (e.g., questionnaires asking about food intake, sport participation or screen time). The operational definition of each outcome (e.g., accelerometer cut points defining PA or SB) was acquired from each publication.

Selection process

Two reviewers (AvD and EJ) independently screened all titles and abstracts of articles identified through the search process for eligibility. If necessary, the full text article was checked for the in- and exclusion criteria. Differences in judgment were resolved through discussion until consensus was reached. Full text of all eligible articles was obtained for further review.

Data extraction

The following data were extracted using a structured form developed for this review (available upon request): (i) general characteristics of the article (author's name, publication year), (ii) study characteristics (design, country), (iii) study population (number, percentage male, mean age at outcome), (iv) method of measurement (objective or self-report) and type of behavior studied, (v) relevant results including measures of associations where possible and (vi) confounders results were adjusted for.

Quality assessment

Two authors (AvD and MC) independently assessed the methodological quality of all included studies, using a 10-item criteria list, adapted from the Effective Public Health

Practice Project Quality Assessment Tool (see Table 4.1).[26] Of the original tool, we deleted three domains that were regarded irrelevant for the included studies. All the studies were cohort studies, so we deleted the domain 'study design'. Further, 'blinding' and 'intervention integrity' were irrelevant for the observational studies, and therefore deleted from the tool. What remains are the five domains that we consider fundamental for an appropriate appraisal of the methodological quality: (i) selection bias, (ii) potential confounding, (iii) method of measurement, (iv) study attrition, and (v) data analysis. Each dimension was judged as strong, moderate or weak, based on predefined criteria. If the study referred to another publication describing the design, study population, psychometric properties of the measurements or other relevant information for the quality assessment, we retrieved the respective publication to score the dimension of concern. We defined high-quality studies as having at least two strong and no weak dimensions, moderate-quality studies as having less than two strong dimensions, but no more than one weak dimension, and low-quality studies as having more than one weak dimension.

Best-evidence synthesis

The included studies were very heterogeneous, especially with regard to the type and measurement of behavior, the categorization of subjects and type of statistical analysis. Therefore, statistical pooling by means of a formal meta-analysis was not feasible, and we performed a best-evidence synthesis. A best-evidence synthesis is a systematic qualitative summarization of available evidence, which helps to reduce the chance of conflicting results and conclusions.[27] We stratified the best-evidence synthesis for studies that are similar with respect to the determinant (birth weight or infant growth) and type of behavior studied. For the best-evidence synthesis, we took the methodological quality into account according to the following decision rules: Strong evidence, provided by generally consistent results in at least two high-quality studies. Moderate evidence, provided by generally consistent results in one high-quality study and at least one moderate- or low-quality study, or generally consistent results in multiple moderate- or low-quality studies. Insufficient evidence, when less than two studies were available or inconsistent findings in multiple studies. Consistent evidence is defined as at least 75% of the findings with similar direction of effect. If there were at least two studies of high methodological quality, we disregarded the studies of low quality in the evidence synthesis; those studies were thus not incorporated in the conclusion.

Table 4.1 Criteria list for the quality assessment

Dimension	Criteria	Judgment rules	
Selection bias	(Q1) Are the individuals selected likely to be representative of the target population? (1) very likely (e.g., randomly selected from target population), (2) somewhat likely (e.g., selected from a source); (3) not likely (e.g., self-referred); (4) can't tell (Q2) What percentage of selected individuals agreed to participate? (1) 80 – 100% agreement; (2) 60 – 79% agreement; (3) less than 60% agreement; (4) not applicable, (5) can't tell	Strong: Moderate: Weak:	Q1 = 1 and Q2 = 1 (Q1 = 1 or 2) and (Q2 = 2 or 4) (Q1 = 3) or (Q2 = 3) or (Q1 = 4 and Q2 = 4)
Confounding	(Q1) Were there important differences between groups? (1) yes; (2) no; (3) can't tell (Q2) If yes, what were the relevant confounders that were controlled for? (1) at least gestational age, sex and age; (2) at least gestational age; (3) not gestational age; (4) can't tell	Strong: Moderate: Weak:	Q1 = 2 or Q2 = 1 (Q1 = 1 or 3) and Q2 = 2 (Q1 = 1 or 3) and (Q2 = 3 or 4)
Measurement	(Q1) Were tools to collect outcome data shown to be valid? (1) yes; (2) no; (3) can't tell (Q2) Were tools to collect outcome data shown to be reliable? (1) yes (objective measures or questionnaires with ICC > 0.7 or Pearson > 0.8); (2) no; (3) can't tell	Strong: Moderate: Weak:	Q1 = 1 and Q2 = 1 (Q1 = 1) and (Q2 = 2 or 3) (Q1 = 2) or (Q1 = 3 and Q2 = 3)
Study attrition	(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group? (1) yes; (2) no; (3) not applicable (i.e. one time surveys or interviews); (4) can't tell (Q2) Indicate the percentage of participants completing the study. (1) 80 -100%; (2) 60 - 79%; (3) less than 60%; (4) not applicable (i.e. retrospective); (5) can't tell	Strong: Moderate: Weak:	Q2 = 1 Q2 = 2 or 4 (Q1 = 4) or (Q2 = 3 or 5)
Data analysis	(Q1) The number of cases was at least 10 times the number of the independent variables. (1) yes; (2) no; (3) can't tell (Q2) Point estimates and measures of variability are presented. (1) yes; (2) no; (3) not applicable	Strong: Moderate: Weak:	Q1 = 1 and Q2 = 1 (Q2 = 2 or 3) or (Q3 = 2 or 3) (Q2 = 2 or 3) and (Q3 = 2 or 3)

Table 4.1 Criteria list, and the corresponding judgment rules for each dimension, for the assessment of the methodological quality of the studies included in this review adapted from the Effective Public Health Practice Project Quality Assessment Tool.[23]

RESULTS

Literature search

The literature search generated a total of 7,907 references: 3,724 in PubMed, 3,061 in EMBASE.com, 577 in PsycINFO and 545 in The Cochrane Library. We consecutively removed duplicates that were selected from more than one database, excluded non-relevant articles by screening the titles and abstracts, and reviewed the remaining articles in full text. (see Figure 4.1) Eventually, 39 articles met the inclusion criteria and were eligible for further analysis.[10-15, 28-35, 37-46, 48-62] Three additional eligible papers[36, 47, 63] were identified through backward and forward citation tracking. Two papers reported exactly the same association based on the same data[56, 63], so the publication with the least additional details[63] was omitted for further analysis. Two studies[11, 62] had overlapping pooled data and partly focused on the same association (i.e., of birth weight with SB), so only the unique results (i.e., of birth weight with PA) of the least comprehensive study[11] was included in the analysis. Table 4.2 provides an overview of the characteristics of the 41 included studies.

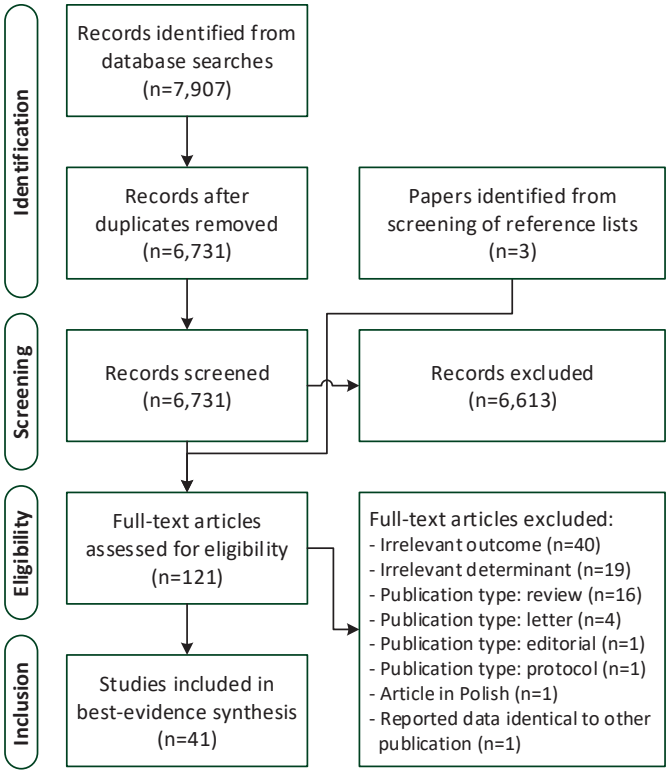

Figure 4.1. Flowchart of the search process and study selection.

Table 4.2 Summary of the studies reporting the association of pre- and postnatal growth with energy balance-related behavior in humans.

Energy intake							
Determinant	**Author, publication year**	**Type of study**	**Population descriptives (n, % male, country)**	**Mean age at time of outcome assessment**	**Outcome (type and method of measurement)**	**Relevant result**	**Adjustment for confounders**
Normal birth weight	**Atladottir, 2000[28]**	Prospective cohort	N=138, 51% male, Iceland	followed through first year of life	Energy intake (dietary record and weighing)	Birth weight was significantly associated with energy intake at the age of 2 months (r=0.20, P<0.05), but not with energy intake at 4, 6, 9 or 12 months.	Sex.
	Barbieri, 2009[29]	Prospective cohort	N=2,050, 48% male, Brazil	24y	Macronutrient intake (questionnaire)	BWR was not associated with total daily energy intake (P=0.43).	GA, sex, BMI, smoking, education, PA, maternal education, maternal income, maternal smoking.
	Boone-Heinonen, 2015[30]	Prospective cohort	N=3,353, 52% male, USA	13.5y	Macronutrient intake (questionnaire)	LBW (BW<2.5 kg) boys had a lower reported energy intake than NBW boys (mean [SE] kcal*day^{-1}: 1981 [118] vs. 2360 [45], P<0.05). HBW (BW>4 kg) boys had a similar energy intake than NBW boys (2506 [129]). There was no significant difference in energy intake between LBW, NBW and HBW girls (1845 [88], 1904 [28], 1823 [92], respectively).	No.
	Dubignon, 1969[31]	Prospective cohort	N=210, 48% male, Canada	Neonatal period	Intake of formula milk over first 4 days of life (direct observation)	Birth weight (ranked and grouped in quartiles) was positively associated with mean daily intake of formula milk in the first 4 days of life (mean ounces per day for increasing birth weight quartiles: 9.9 to 11.5, P_{trend}<0.05).	No.
	Li, 2015[32]	Prospective cohort	N=52,114, 0% male, USA	35.6y	Macronutrient intake (questionnaire)	Total energy intake was not different between ascending birth weight quintiles (mean [SE]: 1,791 [565], 1,779 [746], 1,800 [539], 1,806 [543] and 1796 [558] kcal*day^{-1}, respectively).	No.

Normal birth weight	**Perälä, 2012[33]**	Retrospective cohort	N=1,797, 47% male, Finland	61.5y	Macronutrient intake (questionnaire)	Birth weight was not associated with energy intake (β=221.0 kJ*day^{-1}, 95%-CI: -140.6; 582.6).	GA, sex, age, BMI, education, smoking.
	Ruiz-Narváez, 2014[34]	Prospective cohort	N=21,624, 0% male, USA	38.4y	Energy intake (questionnaire)	Birth weight (categorized as very low, <1,500g, low 1,500-2,499g, normal 2,500-3,999g, and high ≥4,000g) was positively associated with energy intake (mean intake for increasing birth weight categories: 1,493 to 1,516 kcal*day^{-1}; P_{trend}<0.001).	No.
	Shultis, 2005[35]	Prospective cohort	N=1,278, 54% male, United Kingdom	8, 18 and 43 months and 7 years	Diet at age 8, 18, 43 months, and 7 years (dietary record)	There was no association of birth weight with mean daily energy intake at ages 8, 18, 43 months, or 7 years (β up to 18.07 kcal*day^{-1}, 95%-CI: -3.72; 39.86).	GA, sex, age, SES, parental education, birth order, mid-parental height.
Extreme birth weight	**Kaseva, 2013[36]**	Prospective cohort*	VLBW adults, N=151 vs. N=156 controls, 39% male, Finland	22.5y	Mean daily energy intake (dietary record)	There was no difference in total daily energy intake between VLBW adults and NBW controls (P=0.2)	Sex, age, BMI, height, SES, living at parents, smoking and maternal smoking during pregnancy.
	Ounsted, 1975[37]	Prospective cohort	N=191, 54% male, United Kingdom	2 mo	Milk intake (direct observation)	SGA infants consumed more milk per kg body weight, than AGA infants (mean [SD]: 192.4 [37.5] vs. 161.2 [37.2] cc*kg^{-1}). LGA infants consumed less than AGA infants (142.0 [27.1] cc*kg^{-1}, all P<0.05).	No.
Other birth size	**Perälä, 2012[33]**	Retrospective cohort	N=1,797, 47% male, Finland	61.5y	Macronutrient intake (questionnaire)	PI was not associated with energy intake (β=22.0 kJ*day^{-1}, 95%-CI: -18.2; 92.2).	GA, sex, age, BMI, education, smoking.

Infant growth	**Atladottir, 2000[28]**	Prospective cohort	N=138, 51% male, Iceland	followed through first year of life	Energy intake (dietary record and weighing)	Relative growth from birth to 12 months was positively associated with energy intake per kg body weight at the age of 12 months (r=0.30, P<0.01)	Sex.
Short statue after SGA	**Boonstra, 2006[38]**	Retrospective part of intervention study	Children with short statue after SGA. N=88, 41% male, the Netherlands	5.9y	Macronutrient intake (questionnaire)	Children with short stature born SGA had a significantly lower mean (SD) energy intake compared to the recommended-daily intake of age-matched children (1,337 [309] vs. 1,697 [237] kcal, P<0.001).	No.
Eating behavior							
Determinant	**Author, publication year**	**Type of study**	**Population descriptives (n, % male, country)**	**Mean age at time of outcome assessment**	**Outcome (type and method of measurement)**	**Relevant result**	**Adjustment for confounders**
Normal birth weight	**Brown, 2012[39]**	Retrospective observational study	N=298, % male unknown, United Kingdom	18–24 months	Satiety responsiveness and food responsiveness (questionnaire)	No significant association was seen of birth weight with satiety responsiveness or food responsiveness at 18–24 months (data not shown).	Weight, maternal age, maternal education, maternal BMI.

Normal birth weight	**Cardona Cano, 2015[40]**	Prospective cohort	N=3,227, 50% male, the Netherlands.	1.5y, 3y and 6y	Picky eating (questionnaire)	Birth weight was inversely associated with the odds of being a persistent picky eater, with a relative risk ratio of 0.54 per kg increase in birth weight (95%-CI: 0.35; 0.82).	Sex, ethnicity, birth order, maternal age, maternal BMI, maternal education, maternal income, maternal smoking during pregnancy.
	Escobar, 2014†[41]	Prospective cohort	N=196, 52% male, Canada	4y	Emotional overeating (questionnaire)	Children with BWR < 0.85 had a similar emotional overeating score than the other children (difference: 0.40, 95%-CI: -0.64; 1.43).	GA, sex, BMI, mother-child interaction.
	Migraine, 2013[42]	2 prospective cohorts	N=479, 53% male, France	2y	Drive-to-eat score (questionnaire)	Birth weight was inversely associated with drive-to-eat score in the preterm cohort (P=0.001), but not in the term cohort (P=0.10).	GA, sex, duration of breast feeding, maternal age, maternal BMI, maternal education.
	Oliveira, 2015[43]	3 prospective cohorts	N=577-6279, % male not given, UK, Portugal and France	4-6mo, 12-15mo, 24mo and 48-56mo	Feeding difficulties, poor eating, food refusal, difficulties in establishing a daily routine (questionnaire)	70 potential associations were assessed between categories of birth weight (<p10 and >p90; p10-p90 reference) and eating behaviors (4 categories) by age at outcome (4 categories) and cohort (3 categories). There were four significant associations. In the Portuguese cohort, a birth weight under p10 was associated with feeding difficulties (OR 1.73, 95%-CI: 1.09; 2.75) and poor eating (OR 1.98, 95%-CI: 1.98; 2.88) at 4-6mo only and difficulties in establishing a daily routine at 48-54 mo only (OR 1.67, 95%-CI: 1.21; 2.2.31). In the British cohort a birth weight under p10 was associated with feeding difficulties at 4-6mo only (OR 1.26, 95%-CI: 1.05; 1.51).	GA, sex, BMI, type of birth, duration of breastfeeding, number of older siblings, maternal age, maternal BMI, maternal smoking during pregnancy, maternal education.

Normal birth weight	**Silveira, 2012†[44]**	Prospective cohort	N=160, 52% male, Canada	36mo	Impulsive eating (snack delay test)	In girls, but not in boys, a BWR < 0.85 was associated with a lower score on the snack delay test compared to other girls (mean [SE]: 7.76 [0.34] vs. 8.18 [0.13]), no P-value given.	GA, sex, IUGR-status, trial number.
Physical activity							
Determinant	**Author, publication year**	**Type of study**	**Population descriptives (n, % male, country)**	**Mean age at time of outcome assessment**	**Outcome (type and method of measurement)**	**Relevant result**	**Adjustment for confounders**
Normal birth weight	**Andersen, 2009[45]**	Meta-analysis of 13 cohorts	N=43,482, 57% male, Nordic countries	Range 14-66y	Leisure time PA (questionnaire)	Compared with the reference category (3.26–3.75 kg), subjects in the birth weight categories 1.26–1.75, 1.76–2.25, 2.26–2.75, and 4.76–5.25 kg had a lower probability of undertaking leisure time PA, with odds ratios of 0.67 (95%-CI: 0.47; 0.94), 0.72 (0.59; 0.88), 0.89 (0.79; 0.99), and 0.65 (0.50; 0.86), respectively.	GA, sex, age, BMI, educational level, smoking.
	Barbieri, 2009[29]	Prospective cohort	N=2,050, 48% male, Brazil	24y	PA level (questionnaire)	BWR was not associated with the prevalence of inactivity in women (P=0.30) or in men (P= 0.18).	GA, sex, BMI, smoking, education, PA, maternal education, maternal income, maternal smoking.
	Boone-Heinonen, 2015[30]	Prospective cohort	N=3,353, 52% male, USA	13.5y	PA level (questionnaire)	There was no significant difference in reported MET hours per week between LBW (BW<2.5 kg), NBW and HBW (BW>4 kg) adolescents (mean [SE]: 21.0 [1.7], 20.7 [1.1] and 19.0 [2.8] for LBW, NBW and HBW boys, respectively, and 29.9 [3.8], 28.0 [1.2], 28.1 [3.1] for girls).	No.

Normal birth weight	**Campbell, 2010[46]**	Prospective cohort	N=284, 44% male, Jamaica	13.4y	PA level (accelerometry)	Birth weight was not associated with mean c.p.m., (r= -0.081, P=0.2) or percentage above 200 c.p.m. (r=-0.087, P=0.1).	Sex, age, weight, height, pubertal stage.
	Davies, 2006[10]	Retrospective cohort	N=24,874, 70.8% male, United Kingdom	38.0y	% of subjects undertaking regular PA (questionnaire)	Birth weight was positively associated with the likelihood of undertaking regular PA in adulthood (P=0.02).	No.
	Eriksson, 2004[15]	Retrospective cohort	N=500, 37% male, Finland	69.6y	Exercise frequency and intensity, yearly energy expenditure on exercise (questionnaire)	In men, but not in women, birth weight was inversely associated with exercise frequency (P=0.009, effect size not given).	Age, BMI.
	Gopinath, 2013[14]	Prospective cohort	N=1,794, 49% male, Australia. Resurvey at 17-18y: n=1,213	12.7y	Time spent in MVPA (questionnaire)	Birth weight (ranked and grouped in quartiles) was positively associated with total MVPA (mean hours per week for increasing birth weight quartiles: 5.64 to 6.34; P_{trend}=0.02) and outdoor MVPA (4.42 to 5.30; P_{trend}=0.02) among 12-year-old children. At a resurvey at 17-18 years, birth weight was non-significantly positively associated with an increase in total MVPA and outdoor MVPA (P=0.26 and P=0.08, respectively).	GA, sex, age, ethnicity, BMI, parental education, home ownership, exposure to passive smoking.
	Hallal, 2006[47]	Prospective cohort	N=4,453, 49% male, Brazil	10-12y	PA level, % of inactive subjects, defined as <300 min of PA per week (questionnaire)	The percentage of inactive subjects did not differ between subjects grouped in ascending birth weight tertiles (61.9%, 58.1% and 57.5%, respectively, P=0.23). There was a borderline significant positive association between birth weight tertiles and amount of PA per week (210min, 234min and 240min, P=0.05).	No.
	Kehoe, 2012[48]	Prospective cohort	N=415, 49% male, India	7.5y	PA level (accelerometry)	Birth weight was not associated with mean c.p.m. (β=9.62 c.p.m./kg, 95%-CI: -24.73; 43.96).	GA, sex, age, SES, body fat

Normal birth weight	**Li, 2015[32]**	Prospective cohort	N=52,114, 0% male, USA	35.6y	PA level (questionnaire)	Time in MVPA was not different between ascending birth weight quintiles (mean [SE]: 2.5 [3.8], 2.5 [3.9], 2.5 [3.9], 2.5 [2.8] and 2.8 [4.8] hours*week^{-1}, respectively).	No.
	Mattocks, 2008[49]	Prospective cohort	N=5,451, 48% male, United Kingdom	11.8y	PA level (accelerometry)	Birth weight was not associated with mean c.p.m. (β=-0.4 c.p.m.*100g^{-1}, 95%-CI: -6.3; 5.5).	GA, sex, age, maternal education, SES.
	Pahkala, 2010[50]	Prospective cohort	N=346, 59% male, Finland	13y	PA level (questionnaire)	Adolescents in the least active tertile had a birth weight similar to those in the most active tertile (mean [SE]): 3,487 [497] vs. 3,456 [437] for girls and 3,655 [555] vs. 3,637 [490] for boys).	Sex, weight, height, BMI, waist circumference, energy intake.
	Pearce, 2012[51]	Prospective cohort	N=339, 50% male, United Kingdom	8-10y	PA level (accelerometry)	There was no significant association of standardized birth weight with total accelerometry count (r=-0.024, P>0.05) or MVPA (r=0.016, P>0.05).	Sex, season of measurement.
	Ridgway, 2011[11]	Meta-analysis of four cohorts	N=4,170, 44% male, Europe and Brazil	10.2-14.5y	PA level (accelerometry)	There was no significant association of birth weight with mean c.p.m. (β: -1.9 c.p.m.*kg^{-1}, 95%-CI: -12.9; 9.2) or time in MVPA (0.6 min*day*kg^{-1}, 95%-CI: -1.0; 2.1).	Sex, age, BMI, SES.
	Ruiz-Narváez, 2014[34]	Prospective cohort	N=21,624, 0% male, USA	38.4y	Frequency of vigorous exercise (questionnaire)	Birth weight was not associated with frequency of vigorous exercise (P>0.05)	No.
	Said-Mohamed, 2012[52]	Retrospective cohort	N=162, 56% male, Cameroon	4.1y	PA level (accelerometry)	Birth weight was not associated with total PA (β: -0.035 c.p.m.*kg^{-1}, 95%-CI: -0.204; 0.134).	Sex, age, body composition.
	Salbe, 1998[53]	Retrospective cohort	N=88 (of which 24 of diabetic mothers), 50% male, USA	5.5y	PA level (ratio of total energy expenditure [doubly labeled water method] to rest metabolic rate [ventilated hood]).	Although birth weight was higher in children of diabetic than of non-diabetic women (mean [SD]: 3.8 [0.6] vs. 3.5 [0.4] kg, P=0.03), there was no difference in PA level (1.40 [0.12] vs. 1.38 [0.12]).	No.

Normal birth weight	**Van Deutekom, 2015[54]**	Prospective cohort	N=194, 54% male, the Netherlands	8.7y	PA level (accelerometry)	Birth weight was not related to time in MVPA (β=-1.93 min*day^{-1}*SD^{-1}; 95%-CI: -4.53; 0.67).	GA, Sex, age, SES, parental height and BMI, breast feeding, smoking during pregnancy.
	Wijtzes, 2013[55]	Prospective cohort	N=347, 52.4% male, the Netherlands	2.1y	PA level (accelerometry)	Birth weight <2,500g was not associated with percentage of monitored time in MVPA (β=--1.2, 95%-CI: -2.6; 0.2) or mean c.p.m. (β=--77.7, 95%-CI: -177.6; 22.3), compared to birth weight >2,500g.	GA, sex, age, motor development, season of measurement, breast feeding, maternal BMI, number of siblings, daycare attendance, household income.
Extreme birth weight	**Hack, 2012[12]**	Prospective cohort	ELBW children, N=168 vs. 115 controls, 36% male, USA	14.8y	PA level (questionnaire)	ELBW subjects had a significantly lower mean (SD) PA score, compared to NBW controls (2.56 [1.0] vs. 3.05 [0.91], P<0.001).	Sex, ethnicity, SES.
	Kajantie, 2010[56]	Prospective cohort*	VLBW adults, N=136 vs. N=188 controls, 41% male, Finland	22.3y	PA level, divided in occupational, commuting, leisure-time non-conditioning, and leisure-time conditioning PA (questionnaire)	VLBW subjects reported less leisure-time conditioning PA than NBW controls (35.0% vs. 25.0% reporting "not much", 38.0% vs. 25.0% reporting light activity, 22.1% vs. 41.5% reporting brisk activity, P_{trend}=0.0002). VLBW adults report lower frequency (P_{trend}=0.04) and intensity (P_{trend}<0.0001) of PA and shorter average duration of PA sessions (P_{trend}<0.0001). There was no difference in occupational, commuting, or leisure-time non-conditioning PA.	Sex, age, height, lean body mass, body fat percentage, smoking, SES, maternal smoking during pregnancy.

Extreme birth weight	**Kaseva, 2012[13]**	Prospective cohort*	VLBW adults, N=94 vs. N=101 controls, 41% male, Finland	25.0y	PA level, divided in occupational, commuting, leisure-time non-conditioning, and leisure-time conditioning PA, energy expenditure (questionnaire)	VLBW subjects reported less leisure-time conditioning PA than NBW controls, including frequency (mean difference: -38.5%, 95%-CI: -59.8; -7.7), total time (-47.4, 95%-CI: -71.2; -4.1), total volume (-44.3%, 95%-CI -65.8; -9.2) and associated energy expenditure (-55.9%, 95%-CI: -78.6; -9.4). There was no difference in non-conditioning leisure-time PA, commuting PA, high intensity PA and total PA.	Sex, age, BMI, smoking, SES, personality traits.
	Kaseva, 2015[57]	Prospective cohort*	VLBW adults, N=57 vs. N=47 controls, 36% male, Finland	24.7y	PA level (accelerometry)	Between VLBW and NBW adults, there was no difference in daily PA (mean difference: -18.9 c.p.m., 95%-CI: -77.3; 39.5).	Sex, age, BMI, season of measurement, smoking, parental education.
	Rogers, 2005[58]	Prospective cohort	ELBW adolescents, N=53 vs. 31 controls, 41% male, Canada	17.5y	Frequency of sport participation, frequency of PA (questionnaire)	ELBW subjects reported less sport participation than NBW controls (34% vs. 74%, P<0.001), and a lower frequency of PA (P<0.001)	Sex, ethnicity, SES.
	Said-Mohamed, 2012[52]	Retrospective cohort	N=162, 56% male, Cameroon	4.1y	PA level (accelerometry)	Within the range of birth weight > 4.2 kg (n = 11), birth weight is negatively correlated with the time spent in MVPA (r:-0.8, p<0.001).	Sex, age, body composition.
Other birth size	**Eriksson, 2004[15]**	Retrospective cohort	N=500, 37% male, Finland	69.6y	Exercise frequency and intensity, yearly energy expenditure on exercise (questionnaire)	In men, but not in women, PI was inversely associated with exercise frequency (P=0.033), exercise intensity (P=0.030) and energy expenditure on PA (P=0.005, effect sizes not given).	Age, BMI.

Other birth size	**Gopinath, 2013[14]**	Prospective cohort	N=1,794, 49% male, Australia. Resurvey at 17-18y: n=1,213	12.7y	Time spent in MVPA (questionnaire)	There were no significant associations of either birth length or head circumference with MVPA.	GA, sex, age, ethnicity, BMI, parental education, home ownership, exposure to passive smoking.
	Kehoe, 2012[48]	Prospective cohort	N=415, 49% male, India	7.5y	PA level (accelerometry)	Neither birth length, nor head circumference was associated with mean c.p.m. (β=-4.48, 95%-CI: -11.41; 2.45, per cm birth length; β=-1.06, 95%-CI: -10.46; 12.58, per cm head circumference).	GA, sex, age, SES, body fat
	Laaksonen, 2003[59]	Retrospective cohort	N=462, 100% male, Finland	50.6y	PA level (questionnaire)	PI was not associated with duration of strenuous leisure time PA (P_{trend}=0.47) (data not shown).	No.
	Mattocks, 2008[49]	Prospective cohort	N=5,451, 48% male, United Kingdom	11.8y	PA level (accelerometry)	Neither PI nor head circumference was associated with mean c.p.m. (β=1.0, 95%-CI: -3.8; 5.9, per $kg*m^{-3}$ PI; β=-3.5, 95%-CI: -9.2; 2.2, P=0.2 per cm head circumference).	GA, sex, age, maternal education, SES.
Infant growth	**Hallal, 2006[47]**	Prospective cohort	N=4,453, 49% male, Brazil	10-12y	PA level, % of inactive subjects, defined as <300 min of PA per week (questionnaire)	The percentage of inactive subjects did not differ between subjects grouped in ascending mean weight gain at 1-4 years quartiles (58.0%, 57.1%, 58.9% and 58.9%, P=0.52) and mean weight gain at 4-11 years quartiles (61.2%, 54.7%, 55.8%, 61.4%, P=0.58). There was a borderline significant inverse association between mean weight gain at 0-1 year quartiles and percentage of inactive subjects (61.0%, 61.3%, 58.5% and 53.7%, P=0.09).	No.

Infant growth	**Hallal, 2012[60]**	Prospective cohort	N=457, 52% male, Brazil	13.3y	PA level (accelerometry)	Standardized weights at different ages from birth to age four were unrelated to total PA (counts per day). Standardized height at 3 and 12 months were inversely related to total PA (β=-18.0; 95%-CI: -33.0; -2.9, for 3 months. β=-23.4; 95%-CI: -39.7; -7.4, for 12 months).	GA, sex, family income, maternal education, maternal BMI, maternal smoking during pregnancy, all other weight and height variables.
	Robinson, 2013[61]	Retrospective cohort	N=3,217, 52% male, United Kingdom	66.1y	PA score (questionnaire)	Weight gain between birth and 1 year was not associated with PA score (P=0.95).	Sex, birth weight (for infant growth), infant feeding.
	Van Deutekom, 2015[54]	Prospective cohort	N=194, 54% male, the Netherlands	8.7y	Physical activity (accelerometry)	Weight gain between birth and 12 months was not related to time in MVPA (β=-1.12 $min*day^{-1}*\Delta SD^{-1}$; 95%-CI: -3.93; 1.69).	GA, Sex, age, SES, parental height and BMI, breast feeding, smoking during pregnancy.

Sedentary behavior							
Determinant	**Author, publication year**	**Type of study**	**Population descriptives (n, % male, country)**	**Mean age at time of outcome assessment**	**Outcome (type and method of measurement)**	**Relevant result**	**Adjustment for confounders**
Normal birth weight	**Gopinath, 2013[14]**	Prospective cohort	N=1,794, 49% male, Australia. Resurvey at 17-18y: n=1,213	12.7y	Screen time (questionnaire)	Birth weight (ranked and grouped in quartiles) was not associated with screen time (P_{trend}=0.77 at 12 year. P_{trend}=0.48 at 17-18y).	GA, sex, age, ethnicity, BMI, parental education, home ownership, exposure to passive smoking.
	Pearce, 2012[51]	Prospective cohort	N=339, 50% male, United Kingdom	8-10y	SB (accelerometry)	There was no significant association between standardized birth weight and SB (r=0.016, P>0.05).	Sex, season of measurement.
	Said-Mohamed, 2012[52]	Retrospective cohort	N=162, 56% male, Cameroon	4.1y	SB (accelerometry)	Birth-weight is not correlated with time spent in minimal and sedentary activities (data not shown).	Sex, age, body composition.
	Hildebrand, 2015[62]	Meta-analysis of eight cohorts	N=10,793, 47% male, 6 European countries and Brazil	11.5y	SB (accelerometry)	Birth weight was positively associated with mean daily sedentary time (β=4.04 min*kg^{-1}; 95%-CI: 1.14; 6.94).	Sex, age, study, monitor wear time.
	Van Deutekom, 2015[54]	Prospective cohort	N=194, 54% male, the Netherlands	8.7y	SB (accelerometry)	Birth weight was positively associated with sedentary time (β=9.88 min*day^{-1}*SD^{-1}; 95%-CI: 0.74; 19.01).	GA, Sex, age, SES, parental height and BMI, breast feeding, smoking during pregnancy.

Normal birth weight	**Wijtzes, 2013[55]**	Prospective cohort	N=347, 52.4% male, the Netherlands	2.1y	SB (accelerometry)	Birth weight <2,500g was not associated with percentage of time spent in SB, compared to birth weight >2,500g (difference: 2.4%, 95%-CI: -0.4; 5.1).	GA, sex, age, motor development, season of measurement, breast feeding maternal BMI, number of siblings, daycare attendance, household income.
Extreme birth weight	**Kaseva, 2015[57]**	Prospective cohort*	VLBW adults, N=57 vs. N=47 controls, 36% male, Finland	24.7y	SB (accelerometry)	Between VLBW and NBW adults, there was no difference in daily sedentary time (mean difference: 14.1 c.p.m.; 95%-CI: -40.4; 68.5).	Sex, age, BMI, season of measurement, smoking, parental education.
	Said-Mohamed, 2012[52]	Retrospective cohort	N=162, 56% male, Cameroon	4.1y	SB (accelerometry)	In a subgroup of children with birth weight <2,5 kg (n = 10), birth-weight is negatively correlated with time spent in minimal and sedentary activities (r=-0.7, P=0.04).	Sex, age, body composition.
Other birth size	**Gopinath, 2013[14]**	Prospective cohort	N=1,794, 49% male, Australia. Resurvey at 17-18y: n=1,213	12.7y	Screen time (questionnaire)	There were no significant associations of either birth length or head circumference with screen time. (data not shown)	GA, sex, age, ethnicity, BMI, parental education, home ownership, exposure to passive smoking.

Infant growth	**Van Deutekom, 2015[54]**	Prospective cohort	N=194, 54% male, the Netherlands	8.7y	SB (accelerometry)	Infant weight gain was not associated with SB (β=9.30 min*day^{-1}*ΔSD^{-1}; -0.58; 19.18).	GA, Sex, age, SES, parental height and BMI, breast feeding, smoking during pregnancy.

Table 4.2. Description of the study characteristics, study population, type and measurement of behavior, relevant results and confounders results were adjusted for, sorted by energy balance-related behavior and determinant. * Same cohort (Helsinki Study of VLBW adults). † Same cohort. Abbreviations: BW – Birth weight; BWR – Birth weight ratio; BMI – Body Mass Index; LBW – Low birth weight; NBW – Normal birth weight; HBW – High birth weight; MET – Metabolic Equivalent Task; PA – Physical activity; SGA – Small for gestational age (birth weight < -2 SD); AGA – Appropriate for gestational age; LGA – Large for gestational age (birth weight > +2 SD); PI – Ponderal Index; GA – Gestational age; SES – Socio-economic status; VLBW – Very low birth weight (<1500g); MVPA – Moderate-to-vigorous physical activity; ELBW – Extremely low birth weight (≤800g[58] or <1000g[12]); IUGR – Intrauterine growth retardation; c.p.m. – counts per minute; SB – Sedentary behavior.

Study characteristics

Thirty-one (76%) of the 41 studies were prospective cohort studies, nine were retrospective studies and one study combined prospective and retrospective cohorts in a meta-analysis.[45] Four articles assessed energy balance-related behavior in the Helsinki Study of Very Low Birth Weight Adults cohort, of which two articles reported self-reported PA level[13, 56], one reported PA assessed by accelerometry[57] and one reported energy intake.[36] Two articles reported data from the Generation R study. [40, 55] Two articles reported eating behavior in the same cohort of children but at a different age.[41, 44] Five articles combined data of several cohorts[11, 43, 45, 53, 62], two of which described pooled data from the International Children's Accelerometry Database.[11, 62] Thus, we identified data from 35 unique study samples.

The sample size ranged from 84[58] to 43,482 subjects[45], with mean age of the study population ranging from a few days[31] to 70 years.[15] One study included only male subjects[59], and two studies only female subjects.[32, 34] Seven publications reported clinical or otherwise selected populations, namely children with short stature after born small-for-gestational age[38], children with birth weight <1,000g[12] or ≤800g[58] and adults with birth weight <1,500g.[13, 36, 56, 57]

In 39 (95%) of the included studies, birth weight was the primary determinant, expressed as absolute weight, birth weight ratio (i.e., measured birth weight divided by median gestational age adjusted birth weight) or gestational age-adjusted SD-score. Five studies additionally reported other birth size measures besides birth weight (ponderal index, birth length, head circumference, or a combination of these)[14, 15, 33, 48, 49], and one study reported ponderal indices only.[59] Four articles additionally reported the effects of infant growth, besides birth weight.[28, 47, 54, 61] One study addressed only infant growth as primary determinant.[60]

Nine studies reported energy intake as only primary outcome[28, 29, 31, 33, 35-38], three reported energy intake and PA level[30, 32, 34], six reported eating behavior[39-44], 17 reported only PA levels, seven reported both PA levels and SB[11, 14, 51, 52, 54, 55, 57], and one study reported only SB.[62] In 14 of the studies addressing PA and/or SB, the outcome was parent- or self-reported either by questionnaire or interview. In the remainder, PA was objectively assessed by accelerometry.

Thirty-one (76%) of the 41 studies adjusted for a variety of covariates in the analysis. Eleven studies controlled for confounding by gestational age, which was the criterion for moderate quality in the dimension 'potential confounding'.

Quality assessment

The methodological quality of the included studies is presented in Table 4.3. The scoring of the 41 studies led to an initial disagreement in 37 of a total of 205 domains (18%). Disagreement was mainly prevalent in the 'study attrition' domain, because attrition rates were frequently unclearly reported or only mentioned in other publications referred to by the authors. The two reviewers reached consensus on all initial disagreements. Three studies were judged to be of high overall quality[47, 48, 60], 11 studies were of moderate quality, and the remainder of 27 studies was judged to be low overall quality. The most common weakness was the absence of a clear description of the psychometric properties of the measures and not controlling for relevant confounding variables in the analyses.

Associations of birth weight and infant growth with energy balance-related behavior

The results for the various associations of birth weight and infant growth with energy balance-related behavior are summarized in figure 4.2. Because there is some evidence of an age modification of the association of early growth with energy balance-related behavior, with associations only apparent in adult subjects[45], we present the associations stratified by age. Also, we anticipated a possible difference in association between studies with objectively assessed behaviors and studies with self-/parent-reported behaviors, so we present the associations separately for each method of measurement.

Energy intake (figure 4.2A)

According to the best-evidence synthesis, we found no evidence for an association of birth weight with energy intake. This is based on three moderate-quality studies[28, 29, 33] and five low-quality studies[30-33, 35], of which only one low-quality study found a positive association of birth weight with energy intake.[31] Also, the evidence for the association of extreme birth weights with energy intake was inconsistent, as the association of low birth weight was absent in one study[36], positive in another[37] and negative in a third.[34] We found insufficient evidence for an association of other birth sizes or infant growth with energy intake in humans.

Eating behavior (figure 4.2B)

We found no evidence for an association of birth weight with eating behaviors, based on two moderate-quality studies[40, 42] and four low-quality studies.[39, 41, 43, 44] No studies assessed the association of any other of the determinants of interest with eating behavior, resulting in insufficient evidence.

Physical activity (figure 4.2C)

No evidence was found for an association between birth weight and PA in humans. This is based on the results of two studies of high quality[47, 48], five studies of moderate quality[11, 14, 29, 51, 54] and 12 studies of low quality. Fourteen of the 19 studies, including both high-quality studies and all of the studies objectively assessing PA, found no significant association of birth weight with PA. There was also no evidence for an association of other birth sizes[14, 15, 48, 49, 59] or infant growth[47, 54, 60, 61] with later PA. However, four out of five low-quality studies focusing on extreme birth weights found lower PA levels in very high and very low birth weight individuals[12, 52, 56-58], resulting in moderate evidence for an association of extreme birth weights at both ends of the spectrum with lower PA.

Sedentary behavior (figure 4.2D)

There is no evidence for an association of birth weight with SB in humans, based on three moderate-quality and two low-quality studies.[14, 51, 52, 55, 62] However, the one study reporting a positive association of birth weight with SB had a sample size of more than 10,000 subjects[62] compared to 2,642 subjects in the other four studies combined.

There is inconsistent evidence for the association of extreme birth weights with SB, as the association with low birth weight was absent in one study[57] and positive in another. [52] The evidence for the association of other birth sizes and infant growth with SB was insufficient.

Table 4.3 Quality assessment of the included studies

Author, year, reference	Selection bias	Confounding	Measurement	Study attrition	Data analysis	Overall quality	Comment
High-quality studies							
Hallal, 2006[44]	◉	●	●	●	●	●	
Hallal, 2012[45]	◉	●	●	●	●	●	
Kehoe, 2002[46]	◉	●	●	◉	●	●	
Medium-quality studies							
Atladottir, 2000[25]	◉	○	◉	◉	◉	◉	
Barbieri, 2009[26]	●	◉	○	◉	●	◉	
Cardona Cano, 2015 [37]	◉	◉	◉	○	●	◉	
Gopinath, 2013[14]	◉	●	○	◉	●	◉	
Migraine, 2013[39]	○	◉	◉	●	●	◉	
Pearce, 2012[52]	○	●	●	◉	●	◉	
Perälä, 2012[33]	◉	●	○	●	●	◉	
Ridgway, 2011[11]	◉	●	●	○	●	◉	
Silveira, 2012[41]	◉	◉	◉	◉	●	◉	Identical study population as Escobar, 2014
Van Deutekom, 2015[57]	○	●	●	●	●	◉	
Wijtzes, 2013[58]	◉	●	●	○	●	◉	
Low-quality studies							
Andersen, 2009[42]	◉	●	○	○	●	○	
Boone-Heinonen, 2015[27]	◉	○	○	◉	●	○	
Boonstra, 2006[28]	○	○	○	●	○	○	
Brown, 2012[36]	○	○	○	○	○	○	
Campbell, 2010[43]	◉	○	●	○	◉	○	
Davies, 2006[10]	○	○	○	○	◉	○	
Dubignon, 1969[29]	◉	○	●	●	○	○	
Eriksson, 2004[15]	◉	◉	○	○	◉	○	

Author, year, reference	Selection bias	Confounding	Measurement	Study attrition	Data analysis	Overall quality	Comment
Escobar, 2014[38]	◉	◉	○	○	●	○	Identical study population as Silveira, 2012
Hack, 2012[12]	◉	○	○	●	○	○	
Hildebrand, 2015[59]	◉	○	●	○	●	○	
Kajantie, 2010[47]	◉	○	○	◉	●	○	Identical study population as Kaseva, 2012, Kaseva, 2013 and Kaseva, 2015
Kaseva, 2012[13]	◉	○	○	◉	●	○	Identical study population as Kajantie, 2010, Kaseva, 2013 and Kaseva, 2015
Kaseva, 2013[30]	◉	○	○	●	◉	○	Identical study population as Kajantie, 2010, Kaseva, 2012 and Kaseva, 2015
Kaseva, 2015[48]	◉	○	●	○	●	○	Identical study population as Kajantie, 2010, Kaseva, 2012 and Kaseva, 2013
Laaksonen, 2003[49]	○	○	○	○	◉	○	
Li, 2015[31]	◉	○	○	●	◉	○	
Mattocks, 2008[50]	○	○	●	●	●	○	
Oliveira, 2015[40]	◉	◉	○	○	●	○	
Ounsted, 1975[32]	○	○	○	○	○	○	
Pahkala, 2010[51]	○	○	○	○	○	○	
Robinson, 2013[53]	○	○	○	●	●	○	
Rogers, 2005[54]	◉	○	○	◉	◉	○	
Ruiz-Narváez, 2014[34]	○	○	○	●	◉	○	
Said-Mohamed, 2012[55]	◉	○	●	○	●	○	
Salbe, 1998[56]	○	○	●	○	◉	○	
Shultis, 2005[35]	●	●	○	○	●	○	

Table 4.3 Results of the quality assessment of the included studies, with each dimension judged as strong(●), moderate (◉) or weak (○) based on the judgment rules as defined in table 4.1.

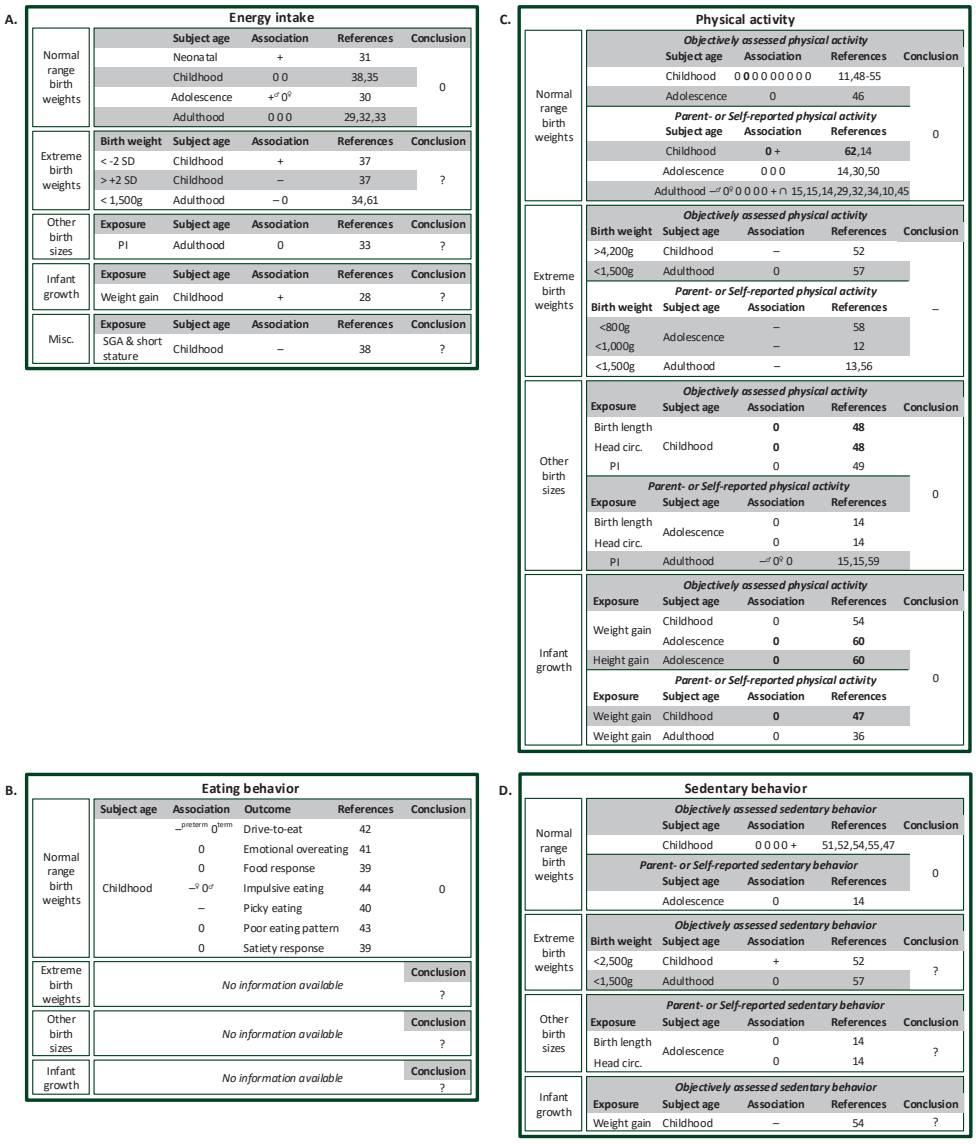

Figure 4.2 Schematic overview of all the available evidence of birth weight and infant growth with energy intake (A), eating behavior (B), physical activity (C) and sedentary behavior (D) in humans described in the literature to date. Each association is represented by + for positive, - for negative, and 0 for no association. ∩ represents an inversed U-shape association. High quality studies are marked in bold. If the association was only present for a subgroup, the subgroup is specified in superscript. The associations are subdivided by subject's age: neonatal (age range: 0-1 mo.), childhood (1 mo.-12 y.), adolescence (12-17 y.) and adulthood (18+ y.). The last column lists the composite score of the best-evidence synthesis: + for positive association, - for negative, 0 for no association and ? for insufficient evidence. Abbreviations: SGA – Small for gestational age; circ. – circumference; PI – Ponderal Index.

DISCUSSION

This review represents the first synthesis of all the available human data on the association of birth weight and infant growth with the spectrum of behaviors that collectively encompass energy balance-related behavior, while accounting for the methodological quality of the studies. We identified 41 eligible studies, of which the large majority focused on the association of birth weight with PA. Overall, there is no evidence for an association of birth weight with PA, SB, energy intake or eating behaviors, although the largest study addressing SB found that a kilogram increase in birth weight was associated with 4 more minutes of daily SB.[62] There was no indication that age modified the association of birth weight with the different outcome measures. The results based on studies with objectively assessed behaviors versus studies with self-/parent-reported behaviors were similar.

Despite evidence supporting the idea that postnatal weight gain is more important than birth weight for later obesity risk[64], the human evidence on the association of infant growth with energy balance-related behaviors is generally insufficient. Four low- and medium-quality studies on infant growth and later PA levels found no evidence for an association, but insufficient evidence was present on the association of infant growth with energy intake, eating behavior or SB.

We found moderate evidence for the association of extreme birth weights with later PA levels, as studies in very low birth weight[13, 56] and extremely low birth weight subjects[12, 58], and a subgroup analysis in subjects with birth weights >4,200g[52], showed lower PA levels in these subjects compared to normal birth weight controls. At present these studies do not allow firm conclusions, due to the paucity of studies and variations in applied birth weight cut-off points. In addition, the extrapolation from conclusions based on subjects with extreme birth weights to the normal birth weight spectrum cannot be done. Prenatal conditions leading to extreme birth weights may have teratogenic or disruptive effects, and the associated comorbidities could lead to poorer motor performance, neurosensory impairments or parental overprotection, which could hamper subjects in their PA participation.[56] The relevance of these disruptive consequences to the origins of energy balance-related behavior in the general population seems remote.

We conducted a best-evidence synthesis to summarize all the available evidence on the association of pre- and early postnatal growth with energy balance related behavior. This has the additional advantage that it accounts for the methodological quality of the studies: low- and moderate-quality studies are disregarded if sufficient high-quality evidence is available. However, this approach does not consider the size of the studies

involved. Many of the studies were relatively small, particularly if samples were stratified by age or sex. For example, in the study of Salbe *et al*. the relatively small sample size of 88 children may have compromised the study's ability to detect an association of birth weight with PA.[53] But in the best-evidence synthesis it carries an equal weight to an individual level meta-analysis of more than 43,000 adult subjects.[45] This latter study found a small but significant inversed U-shaped association between birth weight and PA levels, with odds ratios of being active of 0.67 and 0.65 in the lowest and highest birth weight subjects, respectively, compared to normal birth weight subjects. In another large study of over 10,000 youths, a kilogram higher birth weight was associated with four more minutes of daily SB per kilogram increase in birth weight, which approximates to 1% of mean daily sedentary time.[62] The clinical relevance of these small perturbations in energy balance-related behavior across the normal birth weight range is debatable, but future studies should be of sufficient power to detect small but relevant effect sizes with sufficient confidence. A practical solution may be to combine existing cohort studies in which both simple growth indices and detailed outcome measures have been assessed. These individual level meta-analyses, such as done in the NordNet study[45] and the International Children's Accelerometry Database[62], have been productive in epidemiological research on the developmental origins of obesity to date, and represent a potentially valuable existing resource for future studies on the underlying pathways.

A second limitation of the best-evidence synthesis is that it does not give an estimated overall effect size. For this, a meta-analysis would have been preferable, but this requests statistical pooling. Pooling was only possible for the continuous association of birth weight expressed in kg with PA expressed in accelerometer counts per minute, which was reported in three publications.[11, 48, 49] Øglund *et al*. previously reviewed the literature on the association of birth weight with PA, but their review was limited to studies in children and to studies with PA assessed by accelerometry.[22] They conducted a meta-analysis including these three studies, complemented with unpublished data from two other studies.[46, 55] This meta-analysis of five publications encompassing 18,602 subjects resulted in an overall mean effect size of -3.08 accelerometer c.p.m. per kilogram birth weight (95%CI: -10.2; 4.04), suggesting that there is a very small, non-significant inverse association of birth weight with PA in youth. By another approach this leads to the same conclusion of our best-evidence synthesis of 18 studies, i.e., that there is no evidence for an association of birth weight with PA.

As with any systematic review, this review is limited by the quality of the included studies. The quality of the included studies was generally low, with the exception of 11 studies judged to be of moderate quality, and three studies of high quality. The most common shortcoming in the methodological quality of the included studies was that the required

information to assess the validity and reliability of the behaviors was often lacking or unclearly reported. Reliability and validity of the data may be of particular concern in studies where data were based on recall or self-report albeit using validated instruments.[65] These measurements are prone to misclassification, due to aspects of social desirability and recall bias. We encourage the use of more reliable and valid measures, e.g. accelerometry for the assessment of PA and SB. In addition, more than 40% of the studies scored weak on the quality dimension 'attrition', signaling that the follow-up rate was less than 60% or the drop-outs were not described. A low attrition rate might lead to an overestimation of an association if loss to follow up was differential, for example if VLBW subjects who are limited in their exercise capacity would be more prone to adhere than unimpaired subjects.[56]

Systematic reviews are subject to publication bias. Publication bias typically biases the association away from null, so this might particular be relevant for the (positive) association of extreme birth weights with PA.

Our review was restricted to the association of birth weight and postnatal growth with energy balance-related behaviors as primary outcomes. Therefore, studies focusing on other potentially relevant factors such as basal metabolic rate, its regulatory systems, such as the autonomic nervous system, or closely related pathways, such as the timing of the 'obesity rebound'. Birth weight has been associated with resting metabolic rate[66], and infant weight gain with autonomic nervous system activity.[67] The age of the 'adiposity rebound' (the rise in childhood BMI, after an initial drop, that occurs between age 3 and 6) is considered of critical importance to the setting of energy balance, and empirical evidence suggests that suboptimal perinatal growth advances the timing of adiposity rebound.[68, 69] All these factors have been suggested to contribute to an elevated risk of cardiovascular disease and obesity, and could therefore represent other potential underlying pathways from early growth to later obesity. In addition, we excluded studies relating major gestational food restriction to energy balance-related behaviors. These studies reported that prenatal exposure to the Dutch famine is associated with increased energy intake[70] and less sports participation[71] at middle age. However, these subjects were exposed to environmental stress (war), besides malnutrition, which may induce additional developmental changes. Both prenatal stress and nutritional deprivation are not necessarily accompanied by a reduction in birth weight or change in body composition in early life. Therefore, famine exposure is a unique event, not easily comparable to low birth weight and not generalizable to a suboptimal prenatal environment at present. Therefore, we excluded these studies from the present review.

In conclusion, the studies included in our best-evidence synthesis indicate that there is no evidence for an association of birth weight with PA, SB, energy intake or eating behaviors. Also, there is no evidence that other birth sizes or infant growth are associated with PA in later life. However, there is moderate evidence for an association of extreme birth weights with lower PA. There is insufficient evidence on the associations of infant growth, other birth size measures and extreme birth sizes with energy intake, eating behavior or SB.

Our study leads to important recommendations for future research. First, as a relatively high number of studies found no association of birth weight with any energy balance-related behavior, shifting focus to the effects of infant growth or trimester specific fetal growth[72] on these behaviors might be more fruitful. Second, the association of early growth with energy balance in a broader context, e.g. including basal metabolic rate and adipogenesis, was beyond the scope of this review but will potentially add to the ability to explain the developmental origins of obesity. Third, pooling of data that permit individual level meta-analyses would help ensure sufficient power to detect small perturbations in energy balance.

Obesity prevention and treatment programs may be helped with better identification of mechanisms that underlie relationships between early life growth and adult obesity, but current evidence does not allow inferences about the relation of early-life growth with energy balance-related behavior in later life. First, there is a need of high-quality studies on this topic that overcome the methodological limitations in participation, measurements and attrition rate that almost invariably accompany existing birth cohorts.

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5. THE ASSOCIATION OF BIRTH WEIGHT AND POSTNATAL GROWTH WITH ENERGY INTAKE AND EATING BEHAVIOR AT 5 YEARS OF AGE

A BIRTH COHORT STUDY

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Based on Int J Behav Nutr Phys Act. 2016 Feb 4;13:15

ABSTRACT

BACKGROUND. Low and high birth weight and accelerated postnatal weight gain are associated with an increased risk of obesity. Perinatal effects on energy intake and eating behavior have been proposed as underlying mechanisms. This study aimed to examine the independent associations of birth weight and postnatal weight and height gain with childhood energy intake and satiety response.

DESIGN. In a birth cohort study, we used data from 2,227 children (52% male), mean age 5.6(±0.4) years. Mean daily energy intake and satiety response were parent-reported through validated questionnaires. Exposures were birth weight z-score and conditional weight and height gain between 0-1, 1-3, 3-6, 6-12 months and 12 months to 5 years. Conditional weight and height are residuals of current weight and height regressed on prior growth data, to represent deviations from expected growth. Analyses were adjusted for a set of potential confounding variables.

RESULTS. Conditional weight gain between 1-3, 3-6 months and 12 months to 5 years was significantly associated with energy intake, with 29.7 (95%-CI: 4.6; 54.8), 24.0 (1.8; 46.1) and 79.5 (29.4; 129.7) kcal/day more intake for each Z-score conditional weight gain between 1-3, 3-6 months and 12 months to 5 years, respectively. Conditional height gain between 0-1, 1-3 months and 12 months to 5 years was negatively associated with energy intake (β: -42.0 [66.6; -17.4] for 0-1 months, -35.1 [-58.4; -11.8] for 1-3 months and -37.4 [-72.4; -2.3] for 12 months to 5 years). Conditional weight gain in all periods was negatively associated with satiety response, with effect sizes from -0.03 (-0.06; -0.002) in early infancy to -0.12 (-0.19; -0.06) in childhood. Birth weight was not associated with energy intake or satiety response.

CONCLUSIONS. Our findings suggest that accelerated infant and childhood weight gain are associated with increased energy intake and diminished satiety response at 5 years. Accelerated height gain seems to be beneficial for childhood energy intake. This perinatal 'programming' of energy intake and eating behavior provide a potential mechanism linking early life influences with later obesity and cardiovascular disease.

INTRODUCTION

The alarming rise of childhood obesity world-wide has been identified by the WHO as one of the most serious public health challenges of the 21st century.[1] Secular trends toward increased intake of energy-dense foods and decreased levels of physical activity are recognized as attributable factors to this obesity epidemic, but more recently the perinatal environment has been suggested to play a role. This is based on the observations of numerous population-based cohort studies showing that both low and high birth weight are associated with increased obesity risk.[2] This risk seems to be enhanced when followed by accelerated postnatal weight gain[3], while height gain might protect against subsequent obesity.[4] A proposed explanation for the association of birth weight and postnatal growth with later obesity is through the concept of 'Developmental Origins of Health and Disease', which states that environmental cues during critical periods of life elicit predictive adaptive responses that shape tissue development and metabolic pathways, thereby permanently affecting later health and disease risk.[5] However, the mechanisms by which the perinatal environment influence obesity risk, the relative effects of weight and height gains and which period of postnatal growth has the greatest impact on later health are not well established.

There is clear evidence that nutritional insults during prenatal or early postnatal life can impact hypothalamic development and function, with lasting effects on feeding and metabolism.[6] Therefore, one possible mechanism by which birth weight and direct postnatal growth influence the risk of obesity is that the perinatal environment alters the function of central regulatory mechanisms, including appetite regulation. Animal models were the first to show adult hyperphagia[7-9] and altered feeding behavior[10] in low birth weight offspring, especially when low birth weight was followed by rapid postnatal weight gain. A more recent meta-analysis, however, concluded that there is little effect of prenatal caloric restriction on the programming of appetite in rats, and suggested that the critical window for altering feeding behavior might be located after birth.[11] In humans, only a few studies investigated the early-life effects on later energy intake. Two studies showed that prenatal exposure to the Dutch Famine was associated with increased energy intake at middle age[12, 13], while one study from Brazil observed altered feeding preferences in young women born with low birth weight.[14] However, these studies have been criticized as models of mild nutritional deprivation. In the Brazilian cohort, altered feeding preference was restricted to severely growth impaired individuals, and the Dutch Famine cohorts were exposed to environmental stress (war), besides malnutrition. These stress exposures could also affect behavior, including eating behavior, in later life.[15] In addition, the subjects of most adult cohorts already show an increased rate of obesity and metabolic sequelae, and these metabolic changes may by itself influence eating behavior.

Therefore, it has been noted that differences in energy intake and eating behavior need to be assessed before these metabolic sequelae become apparent, i.e., in childhood.[16] The effects of postnatal growth on later energy intake remain to be addressed.

The aim of the present study was to assess the independent associations of birth weight, postnatal weight gain and postnatal height gain with mean daily energy intake and eating behavior at 5 years of age. In addition, we assessed whether critical postnatal growth periods exist for the association of growth with energy intake and eating behavior by exploring the associations of discrete time intervals in infancy and childhood with these outcomes. We hypothesized that children with low birth weight and subsequent accelerated weight gain, especially in early infancy, have a higher energy intake and a decreased satiety response at 5 years of age.

MATERIALS AND METHODS

Setting

The subjects are participants in the Amsterdam Born Children and their Development (ABCD) cohort, originally consisting of 8,266 pregnant female residents of Amsterdam and their offspring. Details of the study, including its rationale, background and measurements, are described in previous publications.[17] A flowchart of the sampling procedure and attrition rates is available as supplementary figure S5.1. Briefly, the women enrolled in this study completed questionnaires during and after their pregnancy covering sociodemographic data, lifestyle, dietary habits and psychosocial factors, conventional medical and obstetric history, and perinatal details. Of the 6,735 women who gave permission for follow-up of their child, 6,575 mothers also consented to follow up of their child's growth data. Of these children, 3,321 children completed a 'health check' at 5 years of age, at which data on growth and body composition were collected, amongst others. In addition, mothers completed questionnaires about the child's health, development and behavior, and food consumption and eating behaviors.

Written informed consent was obtained from each mother at enrolment and at the age 5 health check. Ethical approval was granted by the Amsterdam Medical Center's Ethics Committee, and all procedures complied with the ethical standards of the Helsinki Declaration.[18]

Assessment of energy intake and eating behavior

Mean daily energy intake and eating behavior of the children were assessed by the Food Frequency Questionnaire (FFQ) and Child Eating Behavior Questionnaire (CEBQ), respectively, completed by the mothers when the children were 5 years of age.

The FFQ approximates mean daily dietary intake based on reported consumption of 71 food items.[19] The questionnaire is developed for Dutch children based on data from the third Dutch National Food Consumption Survey, and validated in children aged 4–6 years.[20] For each food item parents indicated their child's habitual consumption frequency in the previous four weeks by checking one of six frequency categories ranging from 'never' to '6–7 days a week'. Portion sizes were specified in natural units (e.g., one apple), common household measures (e.g., one glass of milk) or grams. The average daily intake of macro- and micronutrients was calculated by multiplying the reported daily intake of each food by its nutrient content, according to the Netherlands Food Composition Table NEVO 2001.[21] Although a comprehensive diet analysis was performed, only the primary variable of interest (i.e., mean daily energy intake) was included in the present statistical analysis.

The CEBQ is a parent-report questionnaire that measures eight dimensions of eating style in children (food responsiveness, enjoyment of food, satiety responsiveness, slowness in eating, fussiness, emotional overeating, emotional undereating, and desire to drink).[22] The 35 items are rated on a 5-point scale, ranging from 'never' to 'always'. For this study, the 'Satiety Response' dimension was used as the outcome measure, as this represents the ability of a child to reduce food intake to compensate for prior foods/snacks to regulate its energy intake, and thereby is of primary interest for this study. This dimension is a composite measure that averages the scores of the following items: "My child has a big appetite", "My child leaves food on his/her plate at the end of the meal", "My child gets full before his/her meal is finished"; "My child gets full easily" and "My child cannot eat a meal if he/she has had a snack just before". A lower score on this dimension reflects a lower satiety response and thus a more disadvantageous eating behavior. The Cronbach's alpha for this dimension was 0.80.

Growth data

Child's sex, birth weight and gestational age at birth were extracted from records from the regional vaccination register (Entadministratie); the office that also performs screening for inborn errors of metabolism in the first week of life. From birth to 12 months of age, child weight and height were ascertained at on average 8 time points as part of the regular preventive Child Health Care in the Netherlands, performed by qualified nurses and physicians.

At age 5, at the ABCD health check, weight and height were measured by a team of trained researchers according to standard protocols using a Leicester portable height measure (Seca, Birmingham, UK) and a Marsden weighing scale (model MS-4102, Rotherham, UK),respectively. Children were dressed in light clothing during these measurements.

Birth weight and subsequent height and weight at 1, 3, 6 and 12 months and 5 years of age were used in the analysis to reflect pre- and postnatal growth. Since most children had no measurements on these exact ages, weight and height data were interpolated to the exact ages of 1, 3, 6 and 12 months by interpolation using individual weight curves. Prior to interpolation, acceptable age windows were defined, which were 0-2, 2-4, 4-8 and 9-15 months for interpolation at 1, 3, 6 and 12 months, respectively. Only children for whom growth data in all acceptable age windows were available as well as birth weight and 5 year measurements were used in the analysis (n=2,533). Birth height was largely missing in our dataset, and therefore not used in the analyses. Data on weight and height were converted to sex-specific weight-for-age and height-for-age Z-scores, respectively, based on the weight and height distributions of the children with complete anthropometric data at all selected ages. Using these Z-scores, we derived growth between successive time points by calculating conditional weight and conditional height variables. The conditional weight and height values are defined as the difference between observed and predicted body size, are uncorrelated by design and are therefore widely used to allow for the high statistical correlation of subsequent weight and height measures at each age.[23, 24] Conditional weight was calculated as the residual from a linear regression of weight at a given age on all prior weights and heights and current height. Conditional height was calculated as the residual from a linear regression of height at a given age on all prior weights and heights but not current weight. The conditional value is thus an independent measure of the deviation in an individual's observed size from its expected size given all prior growth values. A positive conditional value indicates growing faster than expected given prior size.

Assessment of potential confounding variables

Several variables potentially related to birth weight, infant growth and/or eating behavior, such as socio-economic status (SES), ethnicity, maternal and paternal body mass index (BMI), smoking during pregnancy, duration of exclusive breastfeeding, childhood screen time and childhood physical activity (PA) level were considered as potential confounders.[25] SES was based on attained maternal educational level and parent's BMI on self-reported height and weight, collected by questionnaire when the children were 5 years of age. Childhood screen time was based on parents' report of the duration that their child spent watching TV or used a computer or console, scored on a 7-point scale ranging from '(almost) never' to '5 hours/day or more'. PA level was based on parents' responses

to questions on duration of playing outside in summer and winter for weekdays and weekend days separately (0–4 hours/day) and sports participation (0–4 hours/week), which were averaged to produce a PA score (range 0-4) of their child.

Data analysis

Univariate comparisons of basic demographic characteristics and potential confounding factors between the children included in this analysis and those excluded because of insufficient growth data were performed with use of the Student's t-test for continuous variables and the χ^2 test for discrete variables. Descriptive statistics are given as means and SD for continuous data and as frequency distributions for categorical data, unless otherwise stated.

A multivariable linear regression analysis was conducted to assess the association of birth weight, conditional weight variables and conditional height variables with mean daily energy intake and satiety response at age 5. This analysis was adjusted for a set of potential confounding variables: sex, gestational age, ethnicity, maternal and paternal BMI, socio-economic status, smoking during pregnancy, duration of exclusive breastfeeding, current age, height and BMI, screen time and PA level. We present both the unstandardized and the standardized regression coefficients, to provide a better estimate of the magnitude of the association. The distribution of the outcome variables and their residuals was checked for normality and transformations were not deemed necessary.

Because of potential sex differences in the developmental origins of obesity[16], effect modification by sex was assessed by addition of interaction terms.

In a sensitivity analysis, we further assessed how associations found in the primary analyses were influenced or driven by extreme values. Therefore, the analyses were redone excluding the subjects with mean daily energy intakes more than +2SD above the mean or less than -2SD below the mean. In addition, because children born preterm (<37 weeks' gestation) and/or low birth weight (birth weight <-2SD) have substantially different postnatal growth trajectories than children born appropriate-for-gestational age and at term[26], we conducted a sensitivity analysis of the original models excluding these subjects.

Statistical analyses were performed using SPSS Statistics for Windows, Version 17.0. The level of statistical significance was set at 0.05, except for the interaction terms, for which a P-value less than 0.10 was considered significant.

RESULTS

Descriptive statistics

Two thousand two hundred twenty-seven children of the total ABCD cohort had complete data on growth, energy intake and eating behavior available and were included in the final analysis (see supplementary figure S5.1). Relevant baseline characteristics of these children, and a non-response analysis of the remainder of the cohort, are presented in table 5.1. Sex-specific growth and outcome variables are presented in table 5.2. The parent-reported mean daily energy intake in our cohort ranged from 466 to 4,055 kcal/day. This wide distribution was mainly due to a few extreme values, as 98% of the children had an energy intake between 863 and 2,537 kcal/day. Further information about the distribution of the mean daily energy intake is presented in a histogram available as supplementary figure S5.2.

Table 5.1 Characteristics of the study subjects and remainder of the ABCD cohort

n	Study subjects 2,227	Remainder of the cohort 2,904	P value*
Family characteristics			
Ethnicity (%)			<0.01
Dutch	78.7	55.3	
Surinamese	2.4	6.7	
Turkish	1.9	5.0	
Moroccan	3.8	8.6	
Other	13.1	24.4	
Maternal BMI in kg/m^2	23.5 (4.0)	23.7 (4.1)	0.18
Paternal BMI in kg/m^2	24.8 (3.0)	25.2 (3.4)	<0.01
Parental SES (%)			
Low	3.9	6.8	<0.01
Mid	26.7	34.5	
High	69.4	58.8	
Maternal smoking during Pregnancy (% yes)	6.1	7.5	0.03
Duration of exclusive breastfeeding in weeks [median, IQR]	12.0 (20.0)	8.0 (14.0)	<0.01
Subject characteristics - Birth			
Sex (% male)	51.3	49.1	0.11
Gestational age in weeks	40.1	39.5	<0.01
Birth weight in grams	3,570 (501)	3,377 (606)	<0.01
Subject characteristics – Questionnaire data			
Age at FFQ in years	5.7 (0.5)	5.8 (0.5)	<0.001
Mean energy intake in kcal/day	1,530 (338)	1,554 (372)	<0.001
Age at CEBQ in years	5.1 (0.2)	5.3 (0.4)	<0.001
Satiety Response subscore	2.4 (0.5)	2.4 (0.5)	0.25
Screen time in hours/day	1.37 (0.97)	1.56 (1.15)	<0.001
PA score (range 0-4)	1.30 (0.60)	1.22 (0.61)	<0.001

Table 5.1 Descriptive statistics for the study participants and the remainder of the ABCD cohort. Data presented as means and SD in parenthesis unless otherwise stated. Abbreviations: BMI – Body Mass Index; SES – Socioeconomic Status; FFQ – Food Frequency Questionnaire; CEBQ – Child Eating Behavior Questionnaire; PA – Physical Activity. * Student's t-test for continuous variables, Pearson $\chi 2$ for dichotomous variable.

Table 5.2 Descriptive growth and outcome data of the study subjects

N	Boys 1,147	Girls 1,080
Growth Characteristics		
Weight in kilogrammes		
Birth	3.61 (0.50)	3.48 (0.46)
1 months	4.57 (0.55)	4.28 (0.49)
3 months	6.39 (0.68)	5.83 (0.62)
6 months	8.09 (0.82)	7.45 (0.76)
12 months	10.2 (1.0)	9.5 (1.0)
5 years	21.2 (3.0)	21.0 (3.4)
Height in centimetres		
1 months	55.2 (2.0)	54.1 (2.0)
3 months	62.0 (2.0)	60.4 (1.9)
6 months	68.4 (2.1)	66.6 (2.0)
12 months	76.5 (2.4)	74.9 (2.3)
5 years	116.8 (5.5)	116.1 (5.7)
BMI at 5 years in kg/m^2	15.5 (1.3)	15.5 (1.6)
Primary Outcome Measures		
Mean energy intake in kcal/day	1,585 (339)	1,583 (325)
Satiety response subscore	2.3 (0.5)	2.4 (0.5)

Table 5.2 Sex-specific descriptive growth and outcome data for the study participants. Data presented as means and SD in parenthesis.

Primary results

Table 5.3 presents the results of the regression analyses of the association of birth weight, conditional weight and conditional height with mean daily energy intake and satiety response at age 5, fully adjusted for a range of confounders. Conditional weight gain between 1 and 3, and then 3 and 6 months, was positively associated with energy intake, with a 29.7 kcal/day (95%-CI: 4.6; 54.8. P=0.02) and a 24.0 kcal/day (95%-CI: 1.8; 46.1. P=0.03) higher intake at age 5 for every Z-score conditional weight gain between 1-3 months and 3-6 months, respectively. The magnitude of the association between childhood conditional weight gain (i.e., between 12 months and 5 years) and energy intake was approximately 3 times greater (β = 79.5. 95%-CI: 29.4; 129.7. P=0.002). Conditional height gain in early infancy was inversely associated with energy intake: for every Z-score increase in conditional height between 0-1 and 1-3 months, mean daily energy intake was 42.0 kcal (95%-CI: -66.6; -17.4. P<0.001) and 35.1 kcal (95%-CI: -58.4; -11.8. P=0.003) lower at age 5. In addition, there was an inverse association of childhood conditional height gain with energy intake of similar magnitude.

All conditional weight variables had inverse associations with satiety response, with incremental regression coefficients from early infancy to childhood: from a 0.03 lower satiety response score (95%-CI: -0.06; -0.002. P=0.03) for every Z-score increase in conditional weight in the first month of life to a 0.12 lower score (95%-CI: -0.19; -0.06. P<0.001) for every Z-score increase in childhood. Conditional height showed no association with satiety response, and birth weight Z-score was associated with neither mean daily energy intake nor satiety response.

We tested for heterogeneity by sex by including an interaction term of sex with each of the independent variables. All these interaction terms were non-significant (all P>0.10, data not shown), indicating that the associations of birth weight, conditional weight and conditional height with mean daily energy intake and satiety response were similar in boys and girls.

Table 5.3 Association of birth weight, conditional weight and conditional height with mean daily energy intake and satiety response.

	Energy intake (kcal/day) B (95%-CI)	Standardized Beta (95%-CI)	P-value	Satiety Response (score) B (95%-CI)	Standardized Beta (95%-CI)	P-value
Weight						
Birth weight	-7.1 (-30.9; 16.7)	-0.02 (-0.09; 0.05)	0.56	-0.01 (-0.04; 0.02)	-0.02 (-0.08; 0.04)	0.51
Conditional weight 0 – 1 mo	4.5 (-16.1; 25.2)	0.01 (-0.05; 0.08)	0.67	-0.03 (-0.06; -0.00)	-0.06 (-0.12; -0.00)	0.03
Conditional weight 1 – 3 mo	29.7 (4.6; 54.8)	0.09 (0.01; 0.16)	0.02	-0.05 (-0.08; -0.01)	-0.08 (-0.15; -0.01)	0.006
Conditional weight 3 – 6 mo	24.0 (1.8; 46.1)	0.07 (0.01; 0.14)	0.03	-0.04 (-0.07; -0.01)	-0.07 (-0.13; -0.00)	0.01
Conditional weight 6 – 12 mo	8.9 (-14.5; 32.2)	0.03 (-0.04; 0.10)	0.46	-0.07 (-0.10; -0.04)	-0.15 (-0.21; -0.08)	<0.001
Conditional weight 12 mo – 5 y	79.5 (29.4; 129.7)	0.23 (0.08; 0.37)	0.002	-0.12 (-0.19; -0.06)	-0.23 (-0.37; -0.10)	<0.001
Height						
Conditional height 0 – 1 mo	-42.0 (-66.6; -17.4)	-0.13 (-0.20; -0.05)	<0.001	0.01 (-0.02; 0.04)	0.00 (-0.06; 0,06)	0.48
Conditional height 1 – 3 mo	-35.1 (-58.4; -11.8)	-0.11 (-0.18; -0.04)	0.003	0.00 (-0.03; 0.02)	-0.02 (-0.07; 0.04)	0.94
Conditional height 3 – 6 mo	-9.0 (-29.9; 11.9)	-0.03 (-0.09; 0.03)	0.40	-0.02 (-0.05; 0.00)	-0.06 (-0.11; 0.00)	0.06
Conditional height 6 – 12 mo	-9.4 (-31.4; 12.6)	-0.03 (-0.09; 0.04)	0.40	-0.02 (-0.04; 0.01)	-0.04 (-0.09; 0.02)	0.12
Conditional height 12 mo – 5 y	-37.4 (-72.4; -2.3)	-0.11 (-0.21; -0.01)	0.04	-0.02 (-0.05; 0.01)	-0.04 (-0.11; 0.03)	0.24

Table 5.3 Results of the regression analysis of the association of birth weight, conditional weight and conditional height (all in Z-scores) with mean daily energy intake and satiety response at age 5. The coefficients are presented both in the original units of measurement and in standardized betas. Analysis adjusted for sex, gestational age, ethnicity, maternal and paternal body mass index, socio-economic status, smoking during pregnancy, duration of exclusive breastfeeding, current age, height and body mass index, screen time and physical activity score at age 5.

Sensitivity analyses

A sensitivity analysis with children with reported mean daily energy intake less than -2SD below or more than +2SD above the mean excluded (n=88), were consistent with the results of the primary analysis, with slightly broader confidence intervals reflecting the smaller sample size available for analysis. The results of the analyses were also materially unaltered following the exclusion of children born before 37 weeks gestation (n=54), with a birth weight less than -2SD below the mean (n=61), or both (n=59). The results of both sensitivity analyses are available as supplementary table S5.1 and S5.2.

DISCUSSION

In this population-based cohort, we found a higher mean daily energy intake at age 5 in children with conditional weight gain in early infancy (1 to 6 months) and childhood (12 months to 5 years). Conditional height gain in the first 3 months of life or childhood was associated with lower mean daily energy intake at age 5. In addition, conditional weight gain was associated with a lower satiety response, irrespective of the period in which conditional weight gain occurred. Conditional weight gain in childhood had an effect size approximately three times that of conditional weight gain in infancy, both for its association with energy intake and satiety response. These results were adjusted for a range of confounding variables including child's current BMI, and were not driven by outliers or children born preterm or with low birth weight, as the exclusion of these children produced similar results.

To the best of our knowledge, this is the first study in humans describing associations between postnatal growth and later energy intake. The limited literature on early growth and energy intake solely focuses on birth weight, as a marker of prenatal growth. Two independent publications on the health effects of prenatal exposure to the Dutch famine reported that prenatal undernutrition is associated with a preference for an energy-dense diet[12, 13], and in one publication with a higher energy intake at middle age.[13] In addition, an association of severe intra-uterine growth retardation with unfavorable dietary habits were found in a Brazilian and a Finnish cohort of young adults.[14, 27] However, in the only available publication on the association of birth weight with childhood energy intake, Shultis *et al.* found no associations of birth weight with childhood energy intake in a subgroup of the ALSPAC birth cohort.[28] Similarly, a recent study in three prospective birth cohorts found generally no effect of birth weight on eating behaviors in childhood.[29] This is in line with the conclusion of our study that birth weight is not associated with energy intake or satiety response in healthy children. These apparent conflicting results could be explained by the severity of nutritional deprivation, with measurable effects on

later intake only after severe intrauterine growth restriction, or the additive impact of other environmental (war) stressors in the famine cohorts. Another possible explanation arises from the observation that associations of birth weight with energy intake and eating behavior are consistently found in adult cohorts, while studies in children, like ours, found no such association. Low birth weight is associated with features of the metabolic syndrome, especially in adulthood[30], which may secondarily influence dietary habits through an altered secretion of adipokines that control energy balance.[31, 32] Altered adult energy intake may thereby be a direct effect of the metabolic syndrome associated with low birth weight, instead of a mediating link in the pathway of low birth weight to obesity.

Our findings support the hypothesis that postnatal growth influences childhood energy intake, with effect sizes ranging from 24 kcal/day in early infancy to 80kcal/day in childhood for every Z-score conditional weight gain. In contrast, conditional height gain during infancy or childhood seems to protect against excessive energy intake. This is in line with other studies, showing detrimental effects of accelerated weight gain on later body composition[33] and obesity risk[34], while accelerated height gain is associated with a more healthy body composition characterized by an increase in fat-free mass.[35]

Although the effect size of accelerated conditional weight gain may appear small, when considering food consumption even small but chronic excesses in intake could result in a positive energy imbalance resulting in excessive weight gain. For instance, a mathematical model applied to the population of the United States concluded that the obesity epidemic could be explained by an average energy imbalance between intake and expenditure of about 10 kcal/day.[36] In addition, it was estimated that the gradual weight gain of the population of 0.5-1 kg a year over the last two decades can be accounted for by a positive energy imbalance of 15 kcal/day.[37] Therefore, the observed differences in energy intake associated with conditional weight gain could contribute to the increased adiposity risk associated with increased early life growth and hence merit public health attention.

We only found associations of conditional weight and height gain with energy intake for the period of early infancy (first 6 months) and early childhood (1 to 5 years). Although having a different outcome variable, these 'critical periods' for the development of childhood energy intake in our study rather consistently resemble the periods in which weight gain is associated with later body composition. Two studies independently reported that rapid weight gain in early infancy (0–6 months) and early childhood (2/3–6 years), but not in the in-between period, were associated with later body composition.[38, 39] In both studies it was suggested that these periods resemble two different critical periods for the developmental origins of obesity, with different underlying mechanisms

leading to these associations. In early infancy, the development of hypothalamic centers responsible for energy balance are susceptible to environmental cues. For instance, in animal models, perinatal malnutrition was characterized by the induction of central leptin resistance and changes in hypothalamic circuitry, with life-long effects on food intake, energy expenditure and metabolic regulation.[8, 40] In childhood, accelerated weight gain might influence energy intake by the concept of 'adiposity rebound': the rise in BMI after an initial drop that occurs between age 2 and 5. An early onset of this phenomenon is associated with an increased risk of later obesity, independent of other risk factors, and empirical evidence suggests that suboptimal perinatal growth advances the timing of adiposity rebound.[41] Moreover, the age of adiposity rebound is considered of critical importance to the programming of energy balance.[42] Conditional weight gain between 1 and 5 years in our study might thereby reflect an early rise in BMI in the context of an early adiposity rebound, through which eating behaviors and energy intake may be influenced.

Studies are increasingly demonstrating that early life fat accretion, as opposed to a gain in fat-free mass, is implicated in the induction of adult diseases. In our study, infant and childhood weight gain adjusted for height represented a global index of fat accretion. This is common practice in epidemiological studies, because height-adjusted weight gain is consistently associated with increased fat deposition[43, 44], and an increased risk of subsequent obesity.[45] Nonetheless, it represents a very crude index of fat mass, and weight gain has been associated with a gain in fat-free mass as well.[38] Similarly non-specific are birth weight as a marker for prenatal growth and height gain as a marker for fat-free mass. The ABCD study has insufficient longitudinal data based on higher-quality body composition techniques, such as bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA) to address this issue. This implies that future studies of early influences on energy intake or eating behavior should adopt high-quality body composition techniques to assess which body component is critical for the observed effect. However, because in most countries postnatal weight and height is routinely measured on multiple occasions in every child, in contrast to BIA or DXA, its association with obesogenic behaviors has more potential importance for clinical practice and public health, as it allows such growth to be used as a predictor of later risk.

Strengths and weaknesses

A major strength of the current study is the use of a large cohort of apparently healthy boys and girls, with detailed objectively assessed growth data obtained from reliable records. This data is prospectively collected from birth to childhood, which enables exploration of a longitudinal relationship. In addition, we were able to adjust for many known confounders,

such as parental BMI and smoking during pregnancy, and to adjust for height, BMI, screen time and PA, which are known to influence energy intake independent of early growth.

A further strength is the use of conditional growth variables to model growth during discrete time intervals in our cohort. It has been argued that this approach allows for the high correlation of height and size measures, at least partially resolving the problem of collinearity in traditional multiple regression analysis.[23] Our growth measures are, by design, uncorrelated with each other, and the use of Z-scores permits direct comparison of effect sizes across ages.

Several issues in the design and implementation of the study are worth considering. First, we only included children of the ABCD cohort whose weight and height could be estimated for each relevant time point. This reduced the number of eligible children to 2,227, but increased the accuracy of the data analyzed. The accuracy of the estimates depends on accurate measurements of body size and a correct modeling of growth in the ABCD cohort. Measurement errors, outliers and incorrect assumptions of the growth model may potentially impair the accuracy of the estimate. Participation rates were higher among children from higher SES groups and of Dutch descent, so these children were overrepresented in our analysis. Selection bias would be expected to affect the results only if the association of early growth with energy intake and satiety response was different in included children compared with the remainder of the cohort. This is unlikely but cannot be excluded.

Second, the validity of energy intake reporting by the FFQ may be challenged, based on the observation that energy intake is systematically misreported in validation studies of energy intake against objectively measured energy expenditure.[46] In addition, accurate parental assessment of their child's energy intake is hindered by the child's out-of-home food intake.[47] However, a review of validation studies in children concluded that parent-reported energy intake was valid in younger children when compared to doubly-labelled water measured energy expenditure.[48] More specifically to our study, energy intake derived from the FFQ was considered in good agreement to energy expenditure in thirty Dutch children aged 4-6 years, a study population very similar to the children of the ABCD cohort.[20] In addition, a mathematical model to estimate children's energy requirements, taking growth and development into account, estimated that energy intake for 5 year old children would be approximately 1400-1600 kcal/day.[49] This corresponds to the mean parent-reported energy intake of 1530 kcal/day, which suggests that the FFQ is accurate in its estimation of the children's energy intake, at least on a population level. Trabulsi & Schoeller proposed that the removal of implausible energy intake data from the data set could account for potential reporting error[50], but our sensitivity analysis with the

exclusion of outliers did not influence the results. Therefore, we believe that the observed associations are genuine and just, but do acknowledge that potential reporting bias has important implications when attempting to associate early growth with energy intake or satiety response and thus our results should be interpreted with caution.

Third, because of the observational nature of the study with energy intake and satiety responsiveness not measured until 5 years of age, we cannot infer causality. Although the temporal order of our findings suggests an effect of early weight gain on later energy intake and satiety response, a recent study suggested reversed causality: i.e., that infants may already have an increased energy intake and diminished satiety response leading to subsequent increased infant and childhood weight gain.[51] Studies are currently underway that aim to capture feeding practices and eating behaviors from infancy onwards and relate them to future growth.[52] This will provide a better understanding of how and when energy intake and satiety response diverge between rapid infant weight gain subjects and their normal infant weight gain peers.

In conclusion, accelerated infant and childhood weight gain were associated with increased energy intake and eating behavior in childhood, while rapid height gain in early infancy and childhood was associated with reduced childhood energy intake. Future studies on the biological determinants of energy intake and eating behaviors should try to further elucidate the independent associations of infant and childhood height and weight gain, aim to replicate our findings in more diverse socioeconomic and ethnic cohorts and capture energy intake and eating behaviors from an early age onwards to provide further clarification on the directionality of the associations. If future studies confirm the association between early growth and later intake and eating behaviors, these behaviors may be potential mediating factors in the association of early growth with later chronic disease risk. Then, future efforts to prevent childhood obesity through optimization of feeding patterns could in particular focus on children with accelerated infant and childhood weight gain as they are at increased risk of excessive energy intake and detrimental eating behaviors.

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6. THE ASSOCIATION OF BIRTH WEIGHT AND INFANT GROWTH WITH OBJECTIVELY ASSESSED PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR AT 8-9 YEARS OF AGE

THE ABCD STUDY

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Submitted

ABSTRACT

BACKGROUND. Developmental programming of moderate-to-vigorous physical activity (MVPA) and sedentary behavior (SB) may constitute a link between low birth weight, accelerated infant growth and later cardiovascular disease. Therefore, we assessed the independent associations of birth weight and infant growth (in weight, height and body mass index (BMI)) with childhood MVPA and SB.

METHODS. In 2012, we assessed MVPA and SB by accelerometry in a subgroup of 183 children of the Amsterdam Born Children and their Development (ABCD) study, aged 8.6 (±0.4) years. MVPA was defined as minutes per day (min/day) >3000 counts per minute (c.p.m.) and SB as min/day <100 c.p.m. Birth weight was defined as parity-, sex- and gestational age-specific SD, and infant growth as the difference in SD score between birth and 24 months. Infant growth was subsequently subdivided in growth in 0-12 months and 12-24 months. All analyses were adjusted for a range of confounders.

RESULTS. Birth weight was not significantly related to MVPA or SB. Infant weight gain and BMI gain were not significantly associated with MVPA, but for every SD increase in weight between 0-24 months children had 11.9 min/day more SB (95%-CI: 2.2; 21.7). Infant height gain was associated with 3.0 min/day more MVPA per SD increase between 0-24 months (95%-CI: 0.4; 5.6), but not with SB. These associations were similar for growth between 0-12 months, but not 12-24 months.

CONCLUSION. Subjects with accelerated infant weight gain, particularly in the first year, were more sedentary in childhood, while those with increased infant height gain showed more MVPA at 8-9 years. These behaviors may represent a potential modifiable underlying mechanism in the association of early growth with later disease.

INTRODUCTION

Substantial epidemiological evidence has highlighted the importance of early life nutrition on adult-onset disease risk.[1] Low birth weight, as a marker of prenatal undernutrition, is strongly linked to central obesity[2], cardiovascular disease[3] and type 2 diabetes.[4] In addition to low birth weight, high birth weight and accelerated postnatal weight gain have also been associated with cardiometabolic disease and obesity, implying a U-shaped association with disease risk of both early life under- and overnutrition.[5] It is widely believed that these associations reflect physiological predictive adaptive responses to early life environmental cues. These responses lead to permanent adjustments in metabolic systems with lifelong consequences to health and disease risk.[1]

Consideration of how early life nutrition predisposes to adult-onset disease has led to the hypothesis that perinatal nutrition influences the development of behavior related to energy balance and metabolic health. For example, in a rat model, prenatal undernutrition followed by postnatal overfeeding was shown to affect energy balance-related behavior, such as voluntary exercise capacity, as well as body composition and cardiovascular function.[6] Physical activity (PA) is a well-established predictor of fatness level, cardiovascular risk profile and mortality.[7] Independent of PA levels, sedentary behavior (SB) has been shown to be positively associated with an increased risk of type 2 diabetes, and cardiovascular and all-cause mortality in adults.[8, 9] This might indicate that these behaviors provide a pathophysiologic link between low birth weight, accelerated postnatal growth and cardiometabolic diseases.

Human studies on the influence of birth weight on later PA produced inconsistent, even conflicting, results. For example, a meta-analysis comprising >43,000 adolescents and adults, found that both low and high birth weights were associated with lower leisure-time PA levels[10], while other large studies found linear[11] or no[12] association of birth weight with later PA. Evidence on the association of postnatal growth on PA are generally lacking, and there is a call for studies to examine the association of postnatal growth on PA and SB and to assess whether postnatal effects are independent of birth weight.[13]

In the present paper, we examine the independent association of birth weight, as an indicator of fetal growth, and infant growth (expressed as weight, height and BMI gain) with childhood moderate-to-vigorous PA (MVPA) and SB assessed by accelerometry. Second, we assessed whether critical infant growth periods exist for the association with MVPA and SB by exploring the associations of discrete time intervals in infancy with these outcomes. We hypothesize that children born with low birth weight and subsequent accelerated infant weight gain would engage in less MVPA and more SB than other children.

MATERIALS AND METHODS

Setting

This study is embedded in the Amsterdam Born Children and their Development (ABCD) study. The overarching aim of this prospective birth cohort study is to identify prenatal and early life influences on health at birth and in later life.

Full detail of the study design, recruitment of subjects and measures taken since birth are available elsewhere.[14] A flowchart of the sampling procedure and attrition rates is shown in figure 6.1. Briefly, all women pregnant between January 2003 and March 2004 and resident in Amsterdam were eligible to join the study. Of the 12,373 women approached, 8266 participated and completed questionnaires during and after their pregnancies, covering sociodemographic data, lifestyle, dietary habits and psychosocial factors, conventional medical and obstetric history, and perinatal details. Of the 6735 women who gave permission for follow-up of their child, 6575 mothers also consented to follow up of their child's growth data. In 2008, 3321 children completed an 'age 5 health check', at which we collected anthropometric data and parent-reported information about the child's health, development and family characteristics.

In 2012, at 8-9 years of age, a subset of 194 children participated in an add-on study, in which accelerometry data was collected. The rationale of this study and a detailed overview of the study's subjects, design and measurements have been described previously.[15]

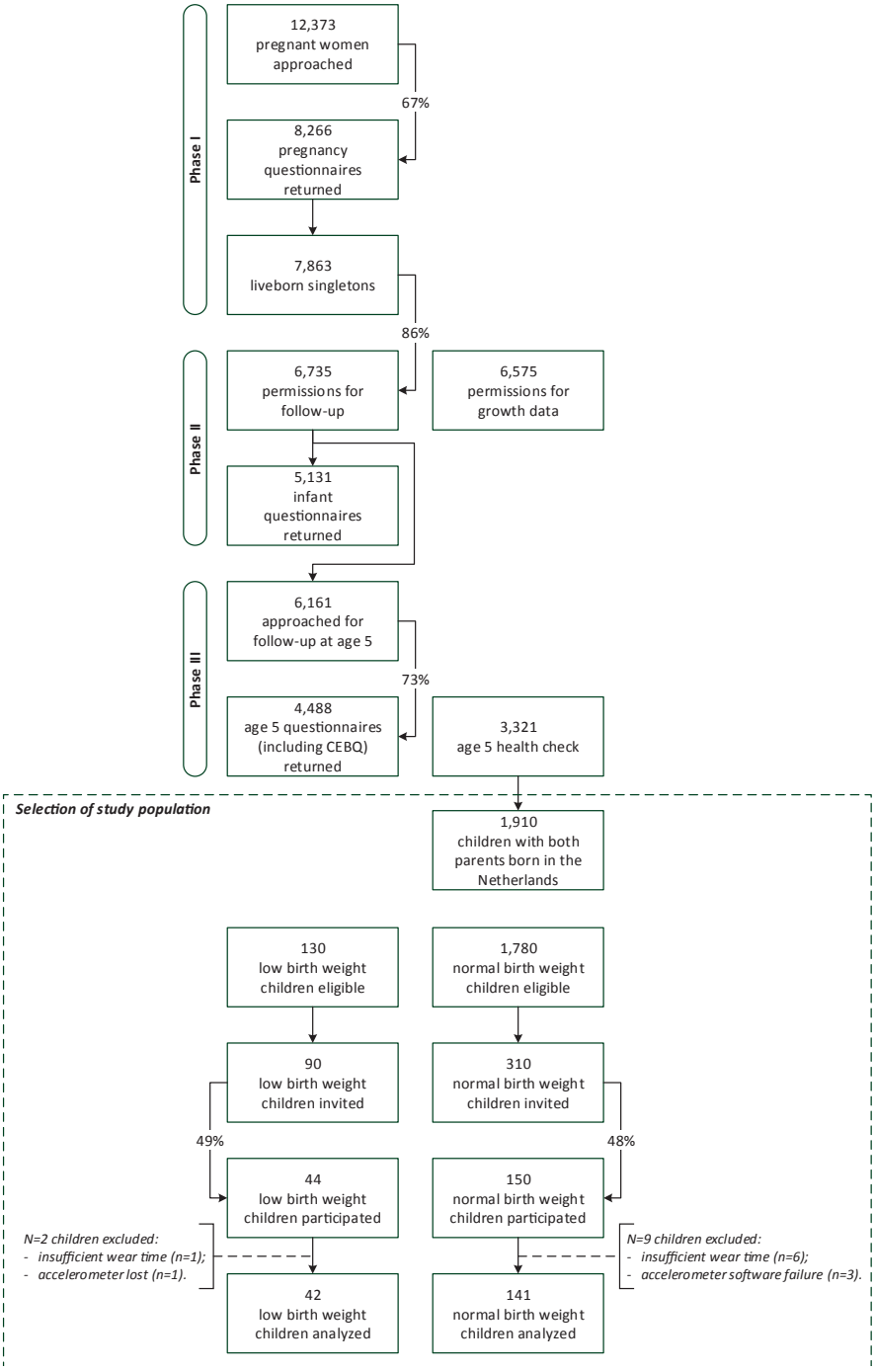

Figure 6.1 Flowchart of the sampling procedure of the ABCD cohort and selection of children included in this study. Low birth weight defined as a birth weight below the tenth parity-, sex- and gestational age-adjusted percentile (-1.28 s.d.).

Study population

For the add-on study in 2012, we randomly selected 400 children from the ABCD birth cohort, for the estimated sample size of 160 children[15] and an expected participation rate of 40%, taking into account the relative low prevalence of low birth weight in our cohort (see figure 6.1). Thus, children with a low birth weight had a higher chance of being selected, to ensure sufficient power to detect the hypothesized difference between low and normal birth weight subjects. Children were eligible for this study if they fully completed the ABCD age 5 health check and were of Dutch ethnicity (i.e., both parents born in the Netherlands) to exclude confounding by ethnicity. All parts of the study were approved by the Amsterdam Medical Center's Ethics Committee and in accordance with the ethical standards of the Helsinki Declaration.

Accelerometry

MVPA and SB were measured using Actigraph triaxial Actitrainers and GT3Xs models (Actigraph LLC, Florida, USA). Accelerometers were attached to the children's waist using an elastic waistband, and the children were told not to remove the device except when sleeping, swimming or bathing, for a period of seven consecutive days.

Raw accelerometer data were manually processed in a standardized manner as previously described.[15, 16] In summary, epoch length was 15 seconds. Non-wear time was defined as more than 60 minutes of consecutive zero counts. Accelerometer data that consisted of at least 8 hours of wear time on at least three schooldays and one weekend day were considered valid and representative for a typical week and were included in further analyses. MVPA was defined as time spent above 3,000 counts per minute (c.p.m.), and SB was defined as time spent below 100 c.p.m., based on cut-off values proposed by Treuth *et al.*[17]

Growth data

Birth weight was obtained from the regional vaccine registration, the office that also routinely performs neonatal screening for inborn errors of metabolism. From birth to 4 years, child weight and height were ascertained at on average 14 time points as part of the regular preventive Child Health Care in the Netherlands, performed by qualified nurses and physicians.

For this add-on study, weight and height were measured by trained researchers according to standard protocols using a Leicester portable height measure (Seca, Birmingham, UK) and a Marsden weighing scale (model MS-4102, Rotherham, UK), respectively, with children dressed in light clothing.

Birth weight is expressed as standard deviation (SD) scores, based on national reference curves adjusted for parity, gestational age, and sex. Infant growth is expressed as the change in SD score for weight, height or BMI between birth and 24 months. Infant growth is subdivided in early and late infant growth, defined as a change in SD score between birth and 12 months, and between 12 and 24 months, respectively.

Data analysis

Descriptive statistics

Continuous data are presented as means with SD and categorical data as frequency distributions. Comparisons between the children included in this study and the remainder of the eligible children (i.e., children of Dutch ethnicity who completed the 'age 5 health check') were made with the use of the Student's t-test for continuous variables and the χ^2-test for discrete variables.

Primary analysis

Relationships between the outcome variables and explanatory factors were assessed by linear regression analysis. First, a univariate analysis with the relevant determinant (birth weight or infant growth, i.e., change in weight, height or BMI SD) and outcome (time spent in MVPA or time spent in SB) was performed (model 1). To account for the high correlation of weight gain with height gain and of successive growth rates, we subsequently adjusted for all prior growth measures, and we adjusted weight gain for height gain (model 2). For example, late infant weight gain (i.e., between 12 and 24 months) was adjusted for birth weight, early infant height and weight gain, and late infant height gain, while late infant height gain was adjusted for birth weight and early infant height and weight gain only. Because BMI already is a measure of the relation of weight and height, we only adjusted BMI gain for birth weight, and prior BMI gain when appropriate. In the third and final model, we additionally adjusted for a set of potential confounding variables, i.e., gestational age, sex, socio-economic status, maternal age, maternal and paternal BMI, days with valid accelerometer data and period during which the accelerometer was worn (to account for weather differences). The analysis for SB was finally adjusted for level of MVPA, and vice versa, to account for their statistical correlation.

Assessment of non-linearity and interactions

Because of a potential U-shaped association of early growth with later PA[10], we assessed the presence of non-linear associations of either birth weight or infant growth with either MVPA or SB by the significance of quadratic terms in polynomial regression analyses. To assess whether the association of birth weight and infant growth exceeds the sum of each exposure separately, we subsequently added an interaction term of birth weight

with infant growth to the model. Because of marked sex differences in the association of early growth with PA, at least in animals[18], effect modification by sex was evaluated by alternately adding a sexbirth weight and sexinfant growth interaction term.

Statistical analyses were performed using SPSS Statistics for Windows, Version 22.0, and statistical tests were set at conventional levels of significance ($P<0.05$), except for the interaction terms and quadratic terms, for which a P-value of less than 0.10 was considered significant.

RESULTS

Descriptive statistics

Of the 400 children invited to take part in this study, 194 participated (see figure 6.1). All 194 children were given an accelerometer. N=7 accelerometers were worn during an insufficient period of time, n=3 had software failure and n=1 was lost, leaving n=183 for analysis. Relevant characteristics of the participants, and comparisons with eligible non-participants, are presented in table 6.1.

Table 6.1 Characteristics of the participants of the study and remainder of the eligible subjects of the ABCD cohort.

N	Included subjects 183		Eligible non-participants 1,727	P value*
Subject characteristics				
Sex (% male)	54.6		49.4	0.26
Gestational age (weeks)	39.7 (2.0)		39.6 (2.0)	0.19
Growth characteristics				
Birth weight (gram)	3,364 (581)		3,490 (559)	<0.01
Birth weight (SD)	-0.29 (1.20)		-0.01 (1.14)	<0.01
Weight gain 0-24 mo (SDS)	0.28 (1.15)		0.00 (1.21)	<0.01
Height gain 0-24 mo (SDS)	0.35 (1.34)		0.03 (1.19)	<0.01
BMI gain 0-24 mo (SDS)	0.14 (1.46)		-0.02 (1.31)	<0.01
Weight gain 0-12 mo (SDS)	0.26 (1.10)		-0.01 (1.15)	<0.01
Height gain 0-12 mo (SDS)	0.11 (0.92)		-0.04 (1.03)	<0.01
BMI gain 0-12 mo (SDS)	0.37 (1.12)		0.06 (1.18)	<0.01
Weight gain 12-24 mo (SDS)	0.04 (0.45)		0.01 (0.55)	0.52
Height gain 12-24 mo (SDS)	0.11 (0.59)		0.08 (0.70)	0.56
BMI gain 12-24 mo (SDS)	-0.04 (0.69)		-0.04 (0.75)	0.90
Family characteristics				
SES (%)				0.04
Low	2.2		6.7	
Mid	21.3		17.8	
High	76.5		75.5	
Maternal age (years)	33.8 (3.5)		31.9 (5.2)	<0.01
Maternal BMI (kg/m2)	22.6 (2.8)		23.2 (3.7)	0.03
Paternal BMI (kg/m2)	25.0 (3.7)		24.8 (2.9)	0.37
Accelerometry data	Boys	Girls		
N	100	83	-	
Age (years)	8.7 (0.4)	8.6 (0.3)	-	
Valid days (median, range)	7 (4 – 7)	7 (4 – 7)	-	
Wear time (hours/day)	11.9 (0.5)	11.9 (0.5)	-	
Time in MVPA (min/day)	43.2 (15.8)	30.3 (10.0)	-	
Time in SB (min/day)	410 (45)	415 (46)	-	

Table 6.1 Characteristics of the study subjects and – when appropriate – for the remainder of the eligible subjects (i.e., children of Dutch ethnicity who completed the ABCD age 5 health check). Data presented as means and SD in parenthesis unless otherwise stated. Abbreviations: SES – Socioeconomic Status; BMI – Body Mass Index. *Student's t-test for continuous variables, Pearson Chi-Square for dichotomous variables.

Table 6.2 Association of birth weight and infant growth (i.e., change in weight, height or BMI SD) with moderate-to-vigorous physical activity and sedentary behavior.

		MVPA (min/day)		SB (min/day)	
		β-coefficient (95%-CI)	**P-value**	**β-coefficient (95%-CI)**	**P-value**
Birth weight (SD) ***n = 183***		-1.0 (-3.1; 1.0)	0.31	2.9 (-2.7; 8.5)	0.31
Infant weight gain	0-24 months	-1.5 (-4.5; 1.5)	0.34	11.9 (2.2; 21.7)	0.02
(ΔSDS)	0-12 mo	2.3 (-2.7; 7.3)	0.37	19.5 (3.2; 35.8)	0.02
n = 183	12-24 mo	1.5 (-3.2; 6.2)	0.52	6.0 (-3.6; 15.6)	0.22
Infant height gain	0-24 months	3.0 (0.4; 5.6)	0.02	0.9 (-8.0; 9.8)	0.84
(ΔSDS)	0-12 mo	2.9 (0.2; 5.6)	0.04	-3.9 (-13.3; 6.2)	0.71
n = 133	12-24 mo	1.9 (-1.6; 5.5)	0.29	6.3 (-5.9; 18.5)	0.31
Infant BMI gain	0-24 months	-1.0 (-3.1; 1.2)	0.38	6.0 (0.4; 11.6)	0.03
(ΔSDS)	0-12 mo	-0.3 (-2.2; 1.7)	0.78	6.4 (0.7; 12.1)	0.03
n = 133	12-24 mo	0.6 (-2.4; 3.6)	0.69	4.1 (-5.8; 14.0)	0.41

Table 6.2 Association of birth weight and growth (i.e., change in weight, height or BMI SD) in different periods in infancy with time in moderate-to-vigorous physical activity and sedentary behavior. Confounder adjusted model, adjusted for prior growth (i.e., infant growth adjusted for birth weight and associations of growth between 12 and 24 months adjusted for growth between 0 and 12 months), concurrent height gain (for weight gain), gestational age, sex, socio-economic status, maternal age, maternal and paternal BMI, number of days with valid accelerometer data (4 – 7 days) and period at which the accelerometer was worn (to account for weather differences). The analysis for SB was finally adjusted for level of MVPA, and vice versa. Abbreviations: MVPA – Moderate-to-vigorous physical activity; SB – Sedentary Behavior; BMI – Body mass index.

Primary analysis

Table 6.2 shows the confounder-adjusted results of the linear regression analyses of birth weight and infant growth (expressed as weight, height or BMI gain) with MVPA and SB (model 3). The results of the univariate analyses (model 1) and prior growth-adjusted analyses (model 2) are presented in a supplementary table S6.1.

Birth weight was not significantly associated with MVPA or SB in our cohort. Infant weight gain (between birth and 24 months) was not significantly associated with MVPA either. However, infant weight gain was significantly associated with SB, with 11.9 minutes per day more sedentary time for every increase in weight SD between birth and 24 months (β: 11.9 min/day/ΔSD, 95%-CI: 2.2; 21.7). Similar associations were observed for BMI gain: there was no significant association of infant BMI gain with MVPA, but a positive association with SB (β: 6.0 min/day/ΔSD, 95%-CI: 0.4; 11.6). Infant height gain between birth and 24 month, however, was positively associated with MVPA (β: 3.0 min/day/ΔSD, 95%-CI: 0.4; 5.6).

The associations of early infant growth (i.e., growth between birth and 12 months) with MVPA and SB echo those of infant growth between birth and 24 months: there were positive associations of infant weight and BMI gain with SB and of infant height gain with MVPA. The effect sizes were similar to those of growth between birth and 24 months, except for the association of weight gain with SB, which was almost twice as long (19.5 min/day/ΔSD, 95%-CI: 3.2; 35.8). The associations of weight, height or BMI gain in late infancy (i.e., between 12 and 24 months) with MVPA or SB were non-significant.

Assessment of non-linearity and interactions

For all analysis, there was no indication of effect modification by sex (all interaction terms P>0.10; data not shown). In addition, the birth weightinfant growth interaction variables were non-significant (P>0.10). There was also no statistical evidence for a non-linear association of any of the growth variables with MVPA or SB (P-value for the quadratic terms > 0.10).

DISCUSSION

To our knowledge, this is the first study on the independent associations of birth weight and infant growth with objectively assessed MVPA and SB during childhood. We found no significant association of birth weight with either MVPA or SB in our cohort of children aged 8-9 years, but a positive association of infant weight gain and infant BMI gain with SB, indicating that children with accelerated weight gain during infancy were more sedentary than their peers with normal infant weight gain rates. Increased infant height gain was associated with more childhood MVPA. These associations were evident after adjusting for a range of potential confounding factors, were similar in boys and girls, and showed no signs of non-linearity.

Interpretation of findings

Several studies linked birth weight to later PA levels, but most of these studies were limited to low birth weight subjects. For example, two independent publications reported lower sports participation[19] and lower exercise intensity and frequency[20] in cohorts of very low birth weight adults. An individual participant data meta-analysis of more than 43,000 subjects revealed an inverted U-shaped relationship between birth weight and PA levels, but this was mainly driven by the low and high extremes of the birth weight spectrum.[10] These extreme birth weights indicate severe prenatal challenges with potentially disruptive effects instead of a physiological predictive adaptive response. In contrast, a recent meta-analysis of population-based studies with normal birth weight subjects concluded that there is no association of birth weight with PA levels.[13] This is

consistent with the main finding of our study, suggesting that childhood PA is not affected by prenatal growth in healthy children.

In a meta-analysis of >10,000 subjects, Hildebrand *et al.* recently reported a small but significant association of birth weight with SB, with a four minute/day increase in sedentary time for each kilogram increase in birth weight.[21] The few other studies that addressed this association invariably reported no association of birth weight with SB[22-24], which complies with the result of our study. However, all studies finding no association of birth weight with SB were considerably smaller, with sample sizes ranging from 105 to 1,213, and the non-significant magnitude of the birth weight-SB association in our study (2.9 min/day more sedentary time per birth weight SD, which equals ~0.5kg) is larger than the effect size reported by Hildebrand. Thus, a lack of power of the other studies, including ours, could also explain the absence of significant findings.

The period in which infant growth can influence later health and disease still receives much deliberation, with some studies highlighting the first year[25] and others considering the first two years of life as the critical period.[26] In our study, we defined infant growth as growth in the first two years of life, and subsequently subdivided this period to assess the independent contributions of growth in the first and second year of life on PA and SB. We showed that the positive associations of infant weight gain and infant BMI gain with SB and of infant height gain with MVPA is fully explained by growth in the first year of life. These findings extend a growing body of literature indicating that especially growth in the first year of life impacts later body composition[27], obesity risk[28] and behaviors closely related to energy balance.[29]

Methodological considerations

To disentangle the independent effects of birth weight, infant height gain and weight gain we developed a statistical model to address the high correlation of weight gain with height gain and of growth rates in successive time intervals. Birth weight was not adjusted for other (subsequent) growth or anthropometric variables, but infant weight gain was adjusted for birth weight and infant height gain. Infant height gain was adjusted for birth weight, and infant weight and height gain in the first year in the case of late infant growth. We adopted this model, because it allows for the evaluation of independent growth periods and is relatively easy to interpret. The coefficient represents the sole effect of weight gain in that time period, independent from any prior growth or height gain. A model with further adjustment for current weight or BMI, which is sometimes advocated[24], would estimate the effect of infant weight gain in children with similar birth weights and childhood weights, thus rather represents an assessment of timing of weight gain rather than the quantity of weight gain.

Strength and Weaknesses

A major strength of our study is that data was collected prospectively from birth to childhood from a large cohort of apparently healthy children. Second, we were able to adjust for many confounders including gestational age and maternal factors, and to assess the independent contributions of birth weight and several indices of postnatal growth, which has not been done to date. Third, we used accelerometers to objectively assess MVPA levels and SB. This provides a more valid and more reliable estimate of MVPA and SB than questionnaires or diaries, which are limited by recall and social desirability bias, misclassification and subjective interpretation.[16] Their relative superior validity and reliability may explain why publications on the association of birth weight with accelerometer-assessed PA invariably report no significant association[12, 23, 30], while studies with self- or parent reported PA often find inverse associations of birth weight with PA.[11, 31, 32]

However, there are some limitations that require consideration when interpreting the findings. First, we examined only a subset of 183 children of Dutch descent in this add-on study. As there are ethnic differences both in growth[33] and SB[34], associations might differ between ethnicities. Also, because low birth weight children were overrepresented in this add-on study, birth weight and infant growth rates differed from the total ABCD cohort. This increased our power to detect significant associations, but limits the generalizability of our results. Therefore, a valuable next step would be to test these associations in an ethnically and anthropometrically more diverse population.

Second, because of the observational nature of the study, we could not infer causality. Although the temporal order of our findings suggest an effect of early weight gain on later SB, it cannot be excluded that these children were already more sedentary in early infancy, contributing to weight gain in the first year of life.

Third, accelerometry to capture PA and SB has limitations on its own. Habitual daily activity of children includes a large variety of activities with movement patterns that are not accurately captured, such as swimming or cycling. The latter may be especially relevant for the Netherlands, thus a risk of bias is acknowledged.

Conclusion and recommendations

In conclusion, birth weight was not significantly associated with MVPA or SB in childhood, but children with increased infant weight and BMI gain showed more SB. Increased infant height gain was associated with more childhood MVPA. These associations were predominantly explained by growth in the first year of life, not the second year. MVPA and SB may thus be potential mediators in the association of early growth with later obesity risk. These findings may have potential clinical and public health implications, as early interventions in a critical period are more likely to have long-term preventive effects.

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7. THE ASSOCIATION OF BIRTH WEIGHT AND INFANT GROWTH WITH PHYSICAL FITNESS AT 8-9 YEARS OF AGE

THE ABCD STUDY

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Based on Int J Obes (Lond). 2015 Apr;39(4):593-600

ABSTRACT

BACKGROUND. Low birth weight and accelerated infant growth are independently associated with childhood obesity. We hypothesized that birth weight and infant growth are associated with physical fitness in childhood, and thereby could act as a link in the developmental origins of obesity. In addition, we assessed whether these associations were mediated by fat-free mass (FFM), moderate-to-vigorous physical activity (MVPA) or sedentary behavior (SB).

METHODS. We assessed physical fitness in 194 children of Dutch ethnicity aged 8.6(±0.35) years from the ABCD cohort. Aerobic fitness was assessed using the 20 meter multistage shuttle run test (20m-MSRT), and neuromuscular fitness using the standing broad jump (SBJ) test and hand grip strength test. MVPA and SB were measured by accelerometry, and FFM by bioelectrical impedance analysis. Low birth weight was defined as below the 10th percentile and accelerated infant growth as a SDS weight gain of >0.67 between birth and 12 months.

RESULTS. Children with low birth weight and subsequent accelerated infant growth attained a lower 20m-MSRT score than the remainder of the cohort, adjusted for multiple confounders ($P<0.01$). Birth weight and infant growth were both independently positively associated with hand grip strength, but not after adjusting for current height and BMI. There was no association of birth weight or infant growth with SBJ. FFM mediated >75% of the association of birth weight and infant growth with hand grip strength, but FFM, MVPA and SB did not mediate the associations with 20m-MSRT.

CONCLUSIONS. Our results indicate that low birth weight and accelerated infant growth might negatively affect childhood aerobic and neuromuscular fitness. Differences in FFM largely explain the developmental origins of neuromuscular fitness. Consequently impaired fitness may constitute a link between low birth weight, accelerated infant growth and obesity. Hence, optimization of fitness in these children may affect their obesity and cardiovascular disease risk.

INTRODUCTION

Numerous epidemiological studies have shown strong and consistent relationships of physical fitness with obesity, cardiovascular disease and all-cause mortality.[1] Of the many dimensions of fitness, the most strongly related to health are aerobic fitness (also known as cardiorespiratory fitness)[2] and neuromuscular fitness (also known as muscle strength).[3] Low levels of aerobic and neuromuscular fitness are considered emerging risk factors for obesity and the metabolic syndrome already in childhood[4] and young adulthood.[5]

Given the importance of physical fitness as a powerful marker of health, recent studies have focused on the determinants of physical fitness and ways in which fitness and its positive effects on health can be maximized and maintained from an early age onwards.[6] The genetic contribution to neuromuscular fitness might be as large as 65%[7], and regular physical activity (PA) increases and maintains fitness at all ages.[8] In addition, more recent evidence suggests a significant contribution of early-life influences on later physical fitness levels. This is in line with the Developmental Origins of Health and Disease (DOHaD)-hypothesis, stating that pre- and early postnatal cues cause developmental adaptations that lead to permanent structural and metabolic readjustments which, in turn, affect later disease risk.[9] As an extension of this hypothesis, studies found that lower birth weight was associated with lower aerobic fitness and reduced muscle strength independent of later body size.[10, 11] These studies indicate that physical fitness may mediate the established associations of low birth weight and accelerated infant growth with adult-onset obesity and cardiometabolic disease. However, so far the evidence is ambiguous, with other studies failing to show an association between birth weight and aerobic fitness.[12, 13] Differences in subject age, sample size, type of fitness test used and severity of growth retardation may explain these inconsistencies.

Both fat-free mass (FFM) and physical activity (PA) have been proposed as potential mediators of the association between birth size, infant growth and physical fitness. Impaired fetal growth has permanent effects on muscle structure and function[10], which in turn could impair running speed or endurance. Recent studies suggest that low birth weight may negatively affect the propensity of undertaking PA, which may also impact physical performance.[14] Prolonged or excessive sedentary behavior (SB) has recently been identified as a potential health risk, independent of PA levels, and a systematic review reported moderate evidence for a longitudinal inverse relationship between sedentary time and aerobic fitness.[15] SB might thereby act as a mediator in associations of birth weight and infant growth with physical fitness, possibly in conjunction with PA or FFM.

The primary aim of our study was to assess the relationship of birth weight and infant growth with aerobic and neuromuscular fitness in a cohort of healthy children aged 8-9 years. The secondary aim was to assess whether these associations were mediated by FFM or objectively-assessed moderate-to-vigorous PA (MVPA) or SB. We hypothesized that low birth weight and accelerated infant growth are associated with lower levels of aerobic and neuromuscular fitness, contributing to the increased risk of obesity and related diseases in later life, and that this association is partly mediated by FFM, MVPA and SB.

MATERIALS AND METHODS

Setting

The present study represents an add-on study in the Amsterdam Born Children and their Development (ABCD) cohort, which was established to assess the long-term impact of prenatal and early-life influences on later health.

The ABCD cohort profile and details of the study design and measures taken since birth have been described previously.[16] In summary, 8266 pregnant woman participated in this study and completed questionnaires during and after their pregnancies, covering sociodemographic data, lifestyle, dietary habits and psychosocial factors, conventional medical and obstetric history, and perinatal details. 6575 mothers also consented to follow up of their child's growth data. In 2008, 3321 children completed an age 5 health check, at which we collected data on growth and body composition and parent-reported information about the child's health, development and family characteristics.

In 2012, at 8 years of age, 194 children of the original cohort participated in an add-on study, in which their physical fitness, MVPA level and SB were characterized. Study design, selection criteria and sample size calculations, and the rationale of the measurements used have been reported previously.[17]

Study population

Of the original cohort, 400 randomly selected children were invited to participate, taking into account the relative small number of low birth weight children. Thus, children with a low birth weight had a double chance to be selected, to ensure sufficient power of the study. Children who (i) fully completed the ABCD age 5 health check and (ii) were of Dutch ethnicity (i.e., both parents born in the Netherlands, to exclude confounding by ethnicity) were eligible for inclusion. Parental informed consent was obtained before enrolment. Ethical approval was granted by the Amsterdam Medical Center's Ethics Committee.

Fitness tests

Consenting children visited one of three test days on which a physical fitness test battery was administered, based on the evidence-based recommendations of the ALPHA[18] and the Eurofit Fitness test Batteries[19] for children and adolescents. We measured isometric muscular strength by means of hand grip strength, explosive muscle strength by means of the standing broad jump (SBJ) test and aerobic fitness by means of the 20 meter multistage shuttle run test (20-m MSRT).

Hand grip strength was measured using a hand dynamometer, with an adjustable grip adjusted to the age- and sex-specific optimal grip span. In the SBJ test, from a starting position immediately behind a line with feet slightly apart, the child jumps as far as possible with feet together. The 20-m MSRT was conducted as described by Léger *et al*.[20], and the attained half-stage at voluntary exhaustion was used as a proxy for aerobic fitness.[21, 22]

Growth data

Child's sex, birth weight and gestational age at birth were obtained from the regional vaccination register (Entadministratie), that also performs routine screening for inborn errors of metabolism in the child's first week of life. From birth to 4 years of age, child weight and height were ascertained at on average 14 time points as part of the regular preventive Child Health Care in the Netherlands, performed by qualified nurses and physicians.

At age 5, at the ABCD health check, and at age 8-9, at the physical fitness test battery, weight and height were measured by a team of trained researchers according to standard protocols using a Leicester portable height measure (Seca) and a Marsden weighing scale (model MS-4102), respectively. Children were dressed in light clothing during these measurements.

Birth weight is expressed as standard deviation (SD) scores, based on national reference curves adjusted for parity, gestational age, and fetal sex[23], with the cut-off value for low birth weight set at the 10^{th} percentile (-1.28 SD). Infant growth is defined as the change in SD score (SDS) between birth and 12 months, with accelerated growth defined as >0.67 change in SDS. Besides growth in weight-for-age, we additionally expressed growth in height-for-age and body mass index (BMI)-for-age, as the association with the outcome may differ between these expressions of growth. The adopted definitions of low birth weight and accelerated infant growth are based on recommendations of Monteiro *et al*.[24], and in line with recent other studies addressing the health effects of perinatal growth.[25, 26]

Assessment of potential mediators

The secondary aim of this study was to assess whether a potential association of birth weight and infant growth with 20-m MSRT, hand grip strength or SBJ test is mediated by FFM, MVPA or SB.

MVPA and SB were objectively assessed by hip-mounted Actigraph accelerometers (models: triaxial Actitrainers or GT3Xs) for seven consecutive days, subsequent to the physical fitness test battery. Accelerometry data was processed as described previously.[17] The cut-off points for MVPA and SB were set at 3,000 and 100 accelerometer counts per minute, respectively.[27]

FFM was previously assessed at the 5 year health check, using arm-to-leg bioelectrical impedance analysis with the Bodystat 1500 MDD machine (Bodystat Inc, Douglas, UK). We used the equations adopted from Kushner *et al*.[28] and Lohman[29] to derive FFM from the electrical impedance.

Assessment of potential confounding variables

Several variables potentially related to birth weight, infant growth and/or physical fitness, such as socio-economic status (SES)[30], duration of exclusive breastfeeding[31], maternal and paternal BMI[32] and smoking during pregnancy[33] were considered as potential confounders. All these variables were collected in previous phases of the ABCD study by self-reported questionnaire responses.

Data analysis

Descriptive statistics are given as means and SD for continuous data and as frequency distributions for categorical data. Univariate comparisons between the children of this add-on study and the non-participating children (i.e., children of Dutch ethnicity attending the ABCD age 5 health check) were made with use of the Student's t-test for continuous variables and the χ^2 test for discrete variables.

Multivariable linear regression analyses were used to assess the association of birth weight and infant growth with attained 20-m MSRT stage, hand grip strength and SBJ test. Because of the inverse correlation between birth weight and infant growth (Pearson's correlation coefficient: -0.70, $P<0.01$), the analysis for birth weight was adjusted for infant growth, and vice versa, enabling us to evaluate the independent effect of both variables (model 1). The model was further adjusted for potential confounders in a group-wise manner: subject-related variables (sex, gestational age, current age, current height, current weight, current BMI; model 2) and family-related variables (SES, maternal height and BMI, paternal height and BMI, maternal smoking during pregnancy, duration of exclusive breastfeeding;

model 3). Because of potential sex differences in the developmental origins of physical fitness[12], effect modification by sex was assessed by addition of an interaction term. Also, we added a birth weight infant growth interaction term to the fully adjusted model, to explore whether the effect of low birth weight and accelerated infant growth exceeds the sum of each exposure separately. P-values less than 0.10 for the interaction term was considered indicative of effect modification.

In order to assess whether FFM, MVPA or SB mediate the association of birth weight and/or infant growth with any of the outcome variables, we conducted a mediation analysis, guided by MacKinnon's multivariate extension of the product-of-coefficients strategy for models involving multiple mediators.[34] We also calculated the percentages of the total effect that was mediated.

Statistical analyses were performed using SPSS Statistics for Windows, Version 17.0, and the level of statistical significance was set at 0.05.

RESULTS

Descriptives

An overall response rate of 48,5% resulted in 194 participating children. Relevant characteristics of the participants, and comparisons with eligible non-participants are presented in table 7.1. Although on average birth weight was lower and infant growth rates higher in the participating group, this was the result of the recruitment strategy, where children with a low birth weight had a higher chance of being selected.

Table 7.1 Characteristics of the participants of the study and eligible non-participants.

N	Participants 194		Eligible non-participants 3457	P value*
Subject characteristics				
Sex (% male)	53.6		49.4	0.26
Gestational age in weeks	39.7 (2.1)		39.6 (2.0)	0.19
Birth weight SD	-0.31 (1.24)		0.04 (1.13)	<0.01
Infant Growth ΔSDS 0-12 months	0.29 (1.15)		-0.05 (1.13)	<0.01
BMI at 5 years in kg/m^2	15.1 (1.07)		15.4 (1.39)	0.01
Family characteristics				
Maternal height in cm	171 (5.7)		171 (7.6)	0.47
Maternal BMI in kg/m^2	22.7 (2.9)		23.0 (3.4)	0.21
Paternal height in cm	184 (7.3)		183 (9.4)	0.34
Paternal BMI in kg/m^2	25.0 (3.1)		24.7 (2.9)	0.25
Parental SES (%)				0.34
Low	3.1		6.7	
Mid	19.1		17.7	
High	77.8		75.4	
Maternal smoking during Pregnancy (% yes)	7.2%		9.8%	0.23
Duration of exclusive breastfeeding in weeks	14.9 (13.4)		13.1 (12.4)	0.06
Physical Fitness test data	Boys	Girls		
N (%)	104	90	-	
Age in years	8.7 (0.4)	8.6 (0.3)	-	0.51
Weight in kg	29.6 (4.0)	29.4 (4.7)	-	0.16
Height in cm	136 (5.9)	134 (5.7)	-	0.87
Physical Fitness test data	Boys	Girls		P value*
BMI in kg/m^2	16.2 (3.6)	16.5 (4.4)	-	0.56
Grip strength in kg	14.5 (3.1)	13.6 (2.7)	-	0.31
SBJ in cm	133 (14.4)	126 (14.0)	-	0.77
20-m MSRT in attained stage	5.9 (1.8)	4.5 (1.2)	-	<0.01
Potential mediating characteristics				
Fat-free mass at 5 years in kg	16.9 (1.7)	16.4 (1.8)		0.03
MVPA in minutes/day	43.5 (15.6)	30.0 (10.2)		<0.01
SB in minutes/day	410 (45)	414 (47)		0.62

Table 7.1 Descriptive statistics for the study participants and the eligible non-participants of the ABCD cohort. Data presented as means and SD in parenthesis unless otherwise stated. Abbreviations: SES – Socioeconomic Status; BMI – Body Mass Index; SBJ – Standing Broad Jump; 20-m MSRT – 20 meter multistage shuttle run test; MVPA – moderate-to-vigorous physical activity; SB – Sedentary behavior. *Student's t-test for continuous variables, Pearson $\chi 2$ for dichotomous variables.

Table 7.2 Association of birth weight and infant growth with aerobic and neuromuscular fitness tests.

	Birth Weight (SDS)		**Infant Growth (ΔSDS in weight 0-12 mo)**	
	β-coefficient (95%-CI)	**P-value**	**β-coefficient (95%-CI)**	**P-value**
20-m MSRT (stage)				
Model 1	-0.13 (-0.40; 0.14)	0.34	-0.28 (-0.58; 0.01)	0.06
Model 2	0.11 (-0.23; 0.45)	0.52	-0.15 (-0.51; 0.20)	0.40
Model 3	0.19 (-0.16; 0.54)	0.28	-0.16 (-0.52; 0.21)	0.39
P-value for interaction term birth weight infant weight gain: <0.001				
Hand grip strength (kg)				
Model 1	0.86 (0.40; 1.31)	<0.001	0.55 (0.06; 1.04)	0.03
Model 2	0.22 (-0.34; 0.78)	0.44	-0.03 (-0.57; 0.52)	0.92
Model 3	0.34 (-0.26; 0.93)	0.26	-0.08 (-0.69; 0.54)	0.81
P-value for interaction term birth weight infant weight gain: 0.60				
Standing Broad Jump (cm)				
Model 1	-0.24 (-2.54; 2.07)	0.84	-1.65 (-4.14; 0.84)	0.19
Model 2	0.96 (-1.97; 3.89)	0.52	-1.23 (-4.10; 1.64)	0.40
Model 3	2.44 (-0.77; 5.66)	0.14	-0.74 (-4.08; 2.60)	0.66
P-value for interaction term birth weight infant weight gain: 0.88				

Table 7.2 Association of birth weight (SDS) and infant growth (weight SDS change between 0 and 12 months) with 20 meter multistage shuttle run test, hand grip strength and standing broad jump test. In addition, the P-value for the interaction term birth weight × infant growth is given. Model 1: Multivariable linear regression analysis with birth weight adjusted for infant growth and vice versa. Model 2: Model 1 additionally adjusted for sex, gestational age, current age, current height, weight and BMI. Model 3: Model 2 additionally adjusted for socio-economic status, maternal and paternal height and BMI, maternal smoking during pregnancy, duration of exclusive breastfeeding.

Primary Analysis

Table 7.2 shows the results of the multivariable linear regression analyses of birth weight and infant growth with the outcome variables: 20-m MSRT score, hand grip strength and SBJ test score. In the infant growth adjusted model, birth weight was not associated with attained stage on the 20-m MSRT or distance jumped on the SBJ test. However, birth weight was significantly associated with hand grip strength, with a 0.86 kg increase in hand grip strength for every SD increase in birth weight (95%-CI: 0.40; 1.31. P<0.001) (model 1). When adjusted for sex, gestational age and current anthropometric properties, the association between birth weight and hand grip strength was reduced and no longer significant (model 2). This was mostly due to strong attenuating effects of current BMI and height on the association.

We further observed a borderline significant inverse association of infant growth with 20-m MSRT score, with a 0.28 lower 20-m MSRT stage for every SD weight gain between birth and 12 months (95%-CI: -0.58; 0.01. P=0.06) (model 1). Adjustment for confounding attenuated the association by approximately 50%, rendering the effect of infant growth on the attained 20-m MSRT stage non-significant (model 2&3). Similarly, infant growth was significantly associated with hand grip strength, with a 0.55kg increase grip strength for every SD increase in infant growth (95%-CI: 0.06; 1.04. P=0.03), but this effect was completely eliminated by adjustment for sex, gestational age and current anthropometric properties.

There was no association of birth weight or infant growth with SBJ test score, before and after adjustment for a range of potential confounding variables.

The interaction terms birth weight sex and infant growth sex were non-significant (all P>0.10, data not shown), indicating that the established associations of birth weight and infant growth with the outcome variables were similar in boys and girls. The interaction term birth weight infant growth, however, yielded a highly significant result (P<0.001) for the 20-m MSRT, indicating effect modification by infant growth for the association of birth weight with 20-m MSRT. There was no indication of effect modification between birth weight and infant growth for hand grip strength or the SBJ test.

To provide a better understanding of the combined effect of birth weight and infant growth on the results of the 20-m MSRT, we dichotomized the growth data based on the earlier defined cut-off points for low birth weight and accelerated infant growth, producing four categories of birth weight/infant growth (figure 7.1). Children with low birth weight and accelerated infant growth attained a 1.02 lower stage on the 20-m MSRT than children with normal birth weight and normal infant growth (95%-CI: 0.23; 1.82. P<0.01), a 1.51 lower stage than children with low birth weight and normal infant growth (95%-CI: 0.51-2.50; P<0.001); and a 1.21 lower stage than children with normal birth weight and accelerated infant growth (95%-CI: 0.30; 2.12; P<0.01). This analysis was adjusted for a broad range of confounding variables, including current BMI, weight and height. There were no significant differences in 20-m MSRT score between the children in the other three categories of growth.

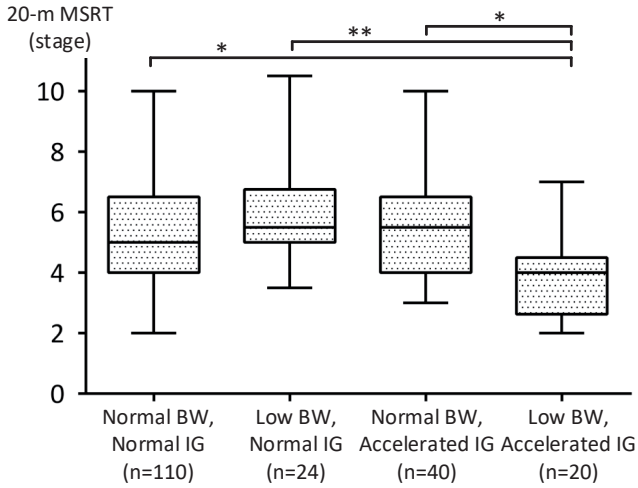

Figure 7.1 Results of the 20 meter multistage shuttle run test by birth weight/infant growth category, as defined in the main text. The numbers below the horizontal axis are the respective group sizes, and the lines and above the figure indicate the significant differences (* P<0.01, ** P<0.001) between the respective groups. Data were analyzed by multivariable linear regression analysis, adjusted for sex, gestational age, current age, height, weight and BMI, socio-economic status, parental height and BMI, duration of exclusive breast feeding and smoking during pregnancy. Abbreviations: 20-m MSRT - 20 meter multistage shuttle run test; BW – Birth weight; IG – Infant growth.

When the models were reran with infant growth defined as the ΔSDS in height or BMI (instead of weight) between birth and 12 months, there were no differences in 20-m MSRT score between any of the four birth weight/infant growth categories (table 7.3). However, infant BMI gain was inversely associated with both hand grip strength and the SBJ test, with a 2.56 cm decrease in SBJ test score (95%-CI: -4.89; -0.23. P=0.03) and a 0.57 kg decrease in hand grip strength (95%-CI: -0.99; -0.16. P=0.007) for every gain in BMI SDS between birth and 12 months, adjusted for a range of confounding variables, including current BMI and height. The analyses for infant height gain showed minimal and non-significant differences to those of the original models.

Table 7.3. Association of infant growth expressed as infant height change and infant BMI change with aerobic and neuromuscular fitness tests.

	ΔSDS in height 0-12 months			ΔSDS in BMI 0-12 months		
	n	β-coefficient (95%-CI)	P -value	n	β-coefficient (95%-CI)	P-value
20-m MSRT (stage)						
Normal BW, normal IG	84	0.86 (-0.13; 1.84)	0.09	63	0.58 (-0.27; 1.43)	0.18
Low BW, normal IG	21	0.89 (-0.28; 2.06)	0.13	16	0.67 (-0.38; 1.72)	0.32
Normal BW, accelerated IG	26	0.86 (-0.25; 1.96)	0.13	47	0.68 (-0.21; 1.57)	0.13
Low BW, accelerated IG	10	*reference*		15	*reference*	
Hand grip strength (kg)	141	-0.28 (-0.86; 0.30)	0.34	141	-0.57 (-0.99; -0.16)	0.007
Standing broad jump (cm)	141	0.34 (-2.85; 3.58)	0.82	141	-2.56 (-4.89; -0.23)	0.03

Table 7.3 Effect of different expressions of infant growth on the association of the four birth weight/infant growth categories with 20 meter multistage shuttle run test, and the association of infant growth with hand grip strength and the standing broad jump test. Shown are the respective group sizes (n), β-coefficients with 95% confidence intervals in parenthesis and significance levels of the fully adjusted models (analogous to model 3 of table 7.2), adjusted for birth weight (when applicable), sex, gestational age, current age, current height, weight and BMI, socio-economic status, maternal and paternal height and BMI, maternal smoking during pregnancy and duration of exclusive breastfeeding. Abbreviations: 20-m MSRT – 20 meter multistage shuttle run test; BW – Birth weight; IG – Infant growth; ΔSDS – difference in standard deviation score.

Mediation Analysis

As a second aim, potential mediation effects of FFM, MVPA and SB on the associations of birth weight and infant growth with the outcome measures were examined. Children with low birth weight and accelerated infant growth attained a 1.11 lower stage on the 20-m MSRT than the other children combined (95%-CI: -1.88; -0.34. P<0.01), but this association was not mediated by FFM, MVPA or SB (figure 7.2). Figure 7.3 shows the associations of birth weight and infant growth with hand grip strength, with full adjustment for confounding except for current height, weight and BMI, as body size might be a proxy for FFM. The significant positive association of birth weight with hand grip strength was almost completely explained by the mediating effect of FFM, accounting for 75,3% of the association (figure 7.3B). The non-significant positive association of infant growth with hand grip strength became negative, after accounting for the mediating effects of FFM (mediating effect >100%). Neither MVPA nor SB mediated the association of either birth weight or infant growth with hand grip strength (mediation effects <1%). Also, there were no mediation effects of FFM, MVPA or SB on the non-significant associations of birth weight and infant growth with the SBJ test (mediation effects <1%; data not shown).

Mediation analyses were also conducted on the associations of infant BMI gain and infant height gain with the outcome measures. No significant mediation effects were observed

of either FFM, MVPA or SB on any of the associations. In particular, there were no mediation effects on the association of infant BMI gain with hand grip strength and SBJ test score (results available as supplementary figures S7.1 and S7.2).

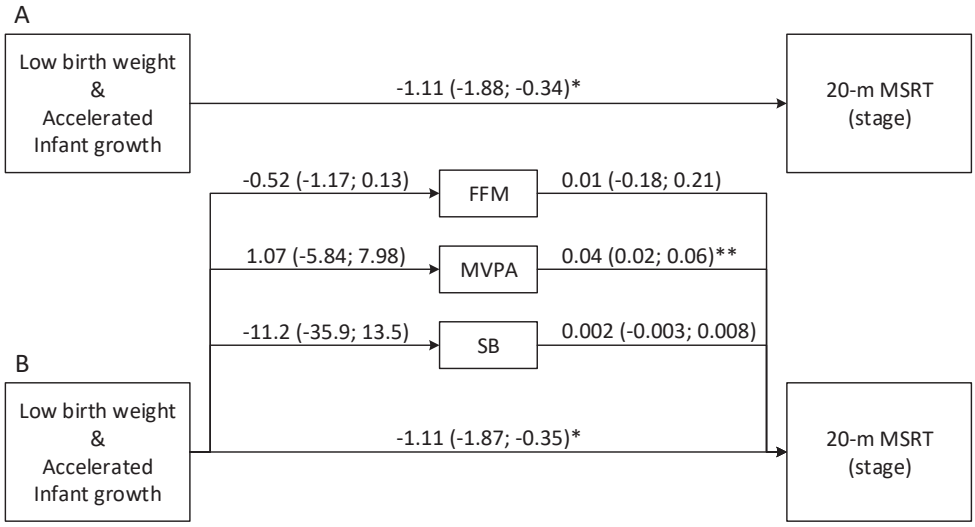

Figure 7.2 A. Total effect (regression coefficient with 95% confidence interval in parenthesis) of low birth weight and accelerated infant growth on the 20 meter multistage shuttle run test, compared to the other birth weight/infant growth categories combined. **B.** Results of the mediation analysis, showing the direct effect (regression coefficient with 95% confidence interval in parenthesis) of low birth weight and accelerated infant growth on the 20 meter multistage shuttle run test, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior. Analysis adjusted for sex, gestational age, current age, height, weight and BMI, socio-economic status, parental height and BMI, duration of exclusive breast feeding and smoking during pregnancy. *P<0.01, **P<0.001. Abbreviations: 20-m MSRT – 20 meter multistage shuttle run test; FFM – fat-free mass; MVPA – moderate-to-vigorous physical activity; SB – Sedentary Behavior.

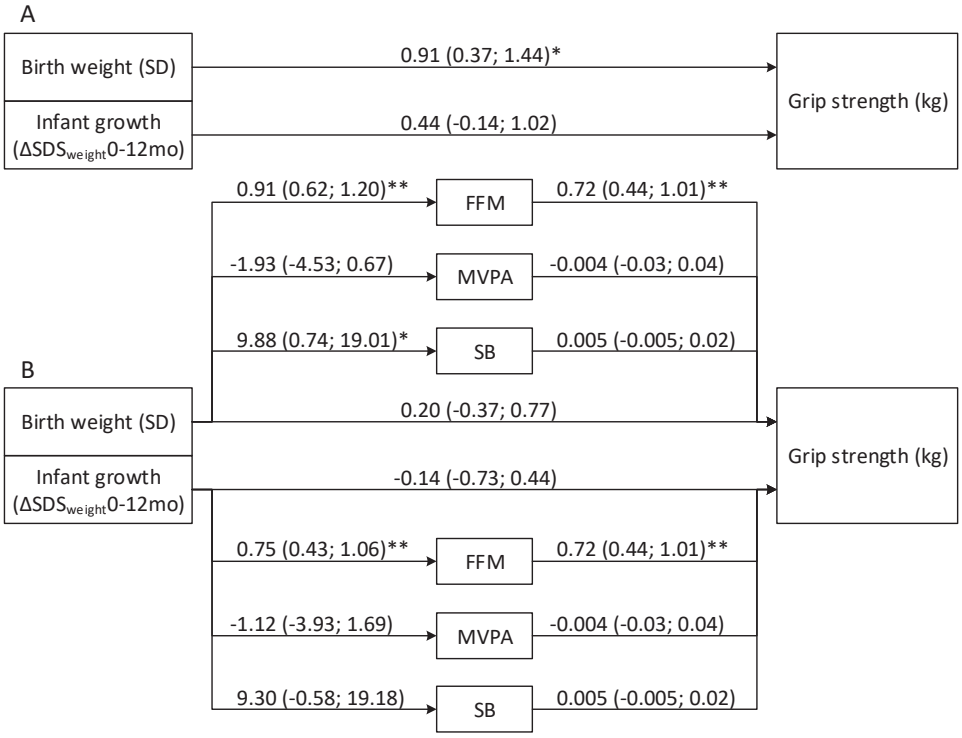

Figure 7.3. A. Individual total effects (regression coefficient with 95% confidence interval in parenthesis) of birth weight and infant growth on hand grip strength. **B.** Results of the mediation analyses, showing the direct effect (regression coefficient with 95% confidence interval in parenthesis) of birth weight and infant growth on grip strength, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior. Analysis adjusted for sex, gestational age, current age, socio-economic status, parental height and BMI, duration of exclusive breast feeding and smoking during pregnancy, but not current BMI, weight or height. *P<0.01, **P<0.001. Abbreviations: SD – Standard Deviation; ΔSDS_{weight}0-12mo – difference in weight standard deviation score between 0 and 12 months; FFM – fat-free mass; MVPA – moderate-to-vigorous physical activity; SB – Sedentary Behavior.

DISCUSSION

As far as we are aware, this is the first population-based study to explore the independent and combined effects of birth weight and infant growth on aerobic and neuromuscular fitness. The relevance of the combined assessment of birth weight and infant growth is particularly evident in the association with aerobic fitness. Children with low birth weight and subsequent accelerated infant growth had lower 20-m MSRT scores, indicating lower aerobic fitness, at 8-9 years of age. This in contrast to children with only low birth weight (with normal infant growth) or only accelerated infant growth (after normal birth weight), who had similar 20-m MSRT scores to children with normal birth weight and normal infant growth. In addition, we found a positive association of birth weight and infant growth with hand grip strength. This was for more than 75% mediated by differences in FFM. Infant growth expressed as BMI gain (instead of weight), however, was negatively associated with both the SBJ test and hand grip strength, but this was not mediated by either FFM, MVPA or SB.

Another common definition of infant growth is the change in weight SDS between 0 and 24 months (instead of 12 months), and several recent articles addressing the DOHaD hypothesis adopt this definition of infant growth.[24] Therefore, we reran our models with the period of infant growth extended to 24 months. The level of significance and magnitude of the differences in hand grip strength and 20-m MSRT score between the low birth weight/accelerated infant growth children and the other children remained similar to our original models, indicating that our findings are robust and not confined to early infancy (data not shown).

Although, to the best of our knowledge, no previous studies addressed the independent and combined effect of birth weight and infant growth on aerobic fitness, a number of studies did examine the effect of birth weight in isolation on aerobic fitness in adults[11, 13], adolescents[12, 14, 35, 36] and children.[14, 30, 35] These studies used different methods to assess aerobic fitness and different definitions of low birth weight, which may explain the mixed findings they report. Salonen *et al.*[13] and Ortega *et al.*[12] found no association between birth weight and aerobic fitness in senior adults and adolescents, respectively. Two other studies, however, did find a positive relationship between birth weight and aerobic fitness in their cohort of adults and 9 year old children, respectively. [11, 30] Boreham *et al.*[35] observed lower fitness scores at 12 years of age with lower birth weights, but the association was eliminated at age 15. Finally, Touwslager *et al.*[36] and Ridgway *et al.*[14] also observed an association between birth weight and aerobic fitness in their respective cohorts of adolescents, although these associations were completely attenuated after adjustment for parental BMI[36] or FFM.[14]

The relationship of birth weight and infant growth with hand grip strength in our study is largely consistent with the existing evidence that has shown independent positive associations of birth weight and early growth with muscle strength, but with attenuation of the relationship after adjustment for later height or BMI.[10, 37] A potential underlying mechanism is that birth weight and infant growth are related to the number of muscle fibers that are established in early growth, and that even later compensating hypertrophy may be inadequate. Indeed, our study shows that the association of birth weight with hand grip strength is largely due to differences in muscle mass, as FFM mediated 75% of the association. Only one other study addressed the role of body composition in the association of birth weight with hand grip strength, and concluded that FFM, derived from skinfold thickness measurements, completely attenuated the observed association of birth weight and hand grip strength.[12] Although their findings, like ours, point to a mediation effect of FFM, the authors did not quantify this effect, nor did they test this hypothesis with a true mediation analysis.

In contrast to the association with hand grip strength, neither birth weight nor infant growth was associated with SBJ. This discrepancy may be explained by the fact that in tests involving jumping, the performance reflects the dimension of work (i.e., the distance through which the weight of the body is moved), not power, and is thereby affected by body weight. This problem cannot be completely solved by controlling for body weight in statistical procedures. The analysis with infant growth expressed as infant BMI gain (instead of weight gain) is less hampered by these statistical difficulties, as BMI reflects a ratio instead of an absolute value. The significant inverse association of infant BMI gain with SBJ test score, with a noticeably large regression coefficient of -2.56cm/ΔSDS, could be the result of a better reflection of changes in body size or proportions with BMI, and further supports the hypothesis that accelerated infant growth negatively influences later neuromuscular fitness.

The mechanisms underlying the association between birth size, infant growth and later fitness levels remain speculative. Several authors suggested that muscle strength might explain the relationship of birth weight with aerobic fitness.[13, 35, 38] Fetal malnutrition could, through its long-lasting effects upon muscle mass and function, result in more rapid fatigue. However, in our cohort differences in FFM could not account for the deficits in aerobic performance in children with low birth weight and accelerated infant growth. Another hypothesis is that differences in PA might explain the association between birth size and later fitness levels[39], as participation in PA is an important determinant of physical fitness in adults[40], and possibly in children.[41] Our study disproves this hypothesis, as mediation analyses showed that none of the associations were mediated by MVPA. In the last decade, SB has been identified as both a determinant of childhood

aerobic fitness and an independent risk factor for obesity.[15] This could indicate a mediating role of SB in the developmental origins of physical fitness. However, our study disproves this hypothesis, as SB did not mediate the observed associations of birth weight and infant growth with physical fitness. Another potential underlying pathway from early growth to fitness is through the timing of 'adiposity rebound': the rise in childhood BMI, after an initial drop, that occurs between age 3 and 6. An early onset of this phenomenon is associated with an increased risk of later obesity, independent of other risk factors, and empirical evidence suggests that suboptimal perinatal growth advances the timing of adiposity rebound.[42] Moreover, the age of adiposity rebound is considered of critical importance to the setting of energy balance.[43] The timing of adiposity rebound could therefore play a mediating role through which perinatal growth affect physical fitness levels. However, this hypothesis was not specifically addressed in this study, partly due to the lack of sufficient childhood growth data in our cohort. Future studies are needed to elucidate the potential role of the adiposity rebound in the developmental origins of physical fitness.

A strength of the ABCD study is that it provides extensive data from a representative cohort of healthy children. The growth data was prospectively collected from birth onwards, giving a reliable and detailed overview of children's growth patterns. The applied physical fitness tests are well known and commonly used, and based on the evidence-based recommendations of the widely accepted ALPHA[18] and Eurofit Fitness test Batteries.[19] We used objective measures to estimate body composition, MVPA and SB. Furthermore, the children have been characterized in detail, enabling us to take account of a large number of potential confounding influences on the associations.

The study also has some limitations that need to be addressed. FFM was assessed at 5 years of age, 3 years prior to the assessment of physical fitness. This could obviously weaken the accuracy of the mediation analysis, as FFM might change during this period. However, a longitudinal study in 7 to 11 year old children found considerable tracking of FFM in childhood (correlation coefficient 0.73).[44] In addition, changes in body composition coincide with changes in BMI, and a moderate to strong correlation of 0.79 was evident between BMI at age 5 and BMI at age 8-9 in our cohort. (data not shown) Therefore, changes in FFM are likely to be small and nonsystematic and unlikely to affect the outcome of the mediation analysis.

Second, we were able to examine only a subset of children of Dutch ethnicity from the total ABCD cohort in this add-on study. As there are ethnic differences both in growth[45] and physical fitness[46], associations might differ in other ethnicities. Also, we studied healthy school children, who actively accepted the invitation to perform physical fitness

testing. This procedure may cause bias towards active, non-obese children, who are more likely to participate. Therefore, future studies should focus on different ethnicities and in more diverse fitness groups to test the robustness of our findings.

In conclusion, our results suggest that low birth weight and accelerated infant growth are associated with lower levels of aerobic and neuromuscular fitness in childhood. In addition, FFM largely mediates the positive association of birth weight and infant growth with neuromuscular fitness, but none of FFM, MVPA or SB mediated the association of low birth weight with subsequent accelerated infant growth with lower levels of aerobic fitness. Because of the strong health effects associated with physical fitness, these findings support early public health strategies to optimize birth weight and infant growth to target later physical performance and potentially later obesity and cardiovascular disease risk associated with suboptimal early-life growth.

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8. THE ASSOCIATION OF BIRTH WEIGHT AND INFANT GROWTH WITH CHILDHOOD AUTONOMIC NERVOUS SYSTEM ACTIVITY AND ITS MEDIATING EFFECTS ON ENERGY BALANCE-RELATED BEHAVIORS

THE ABCD STUDY

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Based on Int J Epidemiol. 2016 Aug;45(4):1079-1090

ABSTRACT

OBJECTIVES. To examine the association of birth weight and infant growth with childhood autonomic nervous system (ANS) activity and to assess whether ANS activity mediates the associations of birth weight and infant growth with energy balance-related behaviors, including energy intake, satiety response, physical activity and screen time.

METHODS. In 2089 children, we prospectively collected birth weight, infant growth defined as conditional weight and height gain between birth and 12 months, and – at 5 years – indices of cardiac ANS activity and parent-reported energy-balance related behaviors. A mediation analysis was conducted, based on MacKinnon's multivariate extension of the product-of-coefficients strategy.

RESULTS. Birth weight and infant height gain were inversely associated with sympathetic, but not parasympathetic, activity at age 5. Infant weight gain was not associated with childhood ANS activity. Infant weight gain was predictive of increased childhood screen time and infant height gain of diminished childhood energy intake, but sympathetic activity did not mediate these associations.

CONCLUSION. Low birth weight children have higher sympathetic activity, which is considered a risk factor for cardiovascular disease. Height gain in infancy seems to be beneficial for childhood sympathetic activity. However, sympathetic activity was no mediator of the associations of infant growth with childhood energy balance-related behaviors. As individual differences in ANS activity predict increased risk of cardiovascular disease, these differences may offer insight into the early life origins of chronic diseases and provide further basis for public health strategies to optimize birth weight and infant growth.

INTRODUCTION

In 1989, Barker and his colleagues reported the inverse association of birth weight with risk of death from cardiovascular disease (CVD), suggesting prenatal factors influence later disease risk.[1] Since then, numerous epidemiological studies found a similar inverse relationship between birth weight and adult-onset diseases, such as CVD[2] , stroke[3] and diabetes.[4] The detrimental effects of low birth weight are exaggerated by rapid postnatal weight gain, further increasing risk of obesity and CVD.[5, 6] These observations led to the 'Developmental Origins of Health and Disease' hypothesis. This hypothesis states that pre- and early postnatal life represents a critical developmental period, during which environmental cues may permanently shape organ structure, neuroendocrine regulation and metabolic function of the fetus, thereby influencing predisposition to adult-onset disease.[7]

Increasing evidence indicates a role for the autonomic nervous system (ANS) in the developmental origins of obesity and CVD.[8] In rat models, prenatal nutritional impairment impacts the hypothalamic-pituitary-adrenal axis and leads to a permanent hyperactivity of the sympathetic nervous system (SNS) and hypoactivity of the parasympathetic nervous system (PNS).[9, 10] Clinical human studies also demonstrated an inverse association between birth weight and SNS activity in adults[11, 12], although a study in neonates born small for gestational age found no such association.[13]

It is well established that the ANS plays a major role in the regulation of metabolic function. SNS is closely linked to systems that regulate blood pressure, glucose metabolism and body weight homeostasis.[14, 15] The vagal neurocircuits of the PNS are vital to the control and regulation of gastrointestinal responses, including satiety, and these responses are considered important for the regulation of energy balance.[16] As such, autonomic imbalance may play an important part in the causation of CVD. For example, increased SNS activity precedes the development of carotid atherosclerosis, increased left ventricular mass, hypertension and obesity, which are all highly predictive of CVD outcomes.[15, 17]

Although it is likely that prenatally induced changes in ANS activity are already apparent in childhood, preceding the development of obesity and CVD, supporting data are not available. In addition, data on the association of postnatal growth with ANS activity are largely unavailable, let alone on the independent contributions of height and weight gain. Third, although ANS function has been repeatedly associated with altered behavior, including increased impulsiveness and greater sensitivity to food reward[18], the mediating effects of ANS activity on energy-balance related behaviors have yet to be described.

In the present study, we examined the independent association of birth weight, infant weight gain and infant height gain with ANS activity at 5 years of age. As a secondary aim, we assessed whether ANS activity mediates the associations of birth weight, infant weight gain and infant height gain with energy balance-related behaviors, i.e., energy intake, satiety response, physical activity and screen time.

METHODS AND DESIGN

Setting

This study is part of the Amsterdam Born Children and their Development (ABCD) study, a prospective birth cohort study aimed at the identification of prenatal and early life influences on later health. The design and conceptual framework of the ABCD study are described in detail in previous publications.[19] The study procedure and participation rates are illustrated in figure 8.1. Briefly, the ABCD study included 8266 pregnant women between January 2003 and March 2004. After delivery, birth weight of the children was obtained from the regional vaccine registration (Entadministratie), the office that also performs neonatal blood screening for inborn errors of metabolism, as is routinely performed in the Netherlands in the 1st week of life. Until the age of 4 years, height and weight measures of these children were routinely collected as part of regular preventive Child Health Care.

In 2008, around their 5th birthday, 3321 children completed a 'health check'. At this health check, all children underwent anthropometric measurements and assessment of ANS activity, as described below. In addition, parents completed questionnaires about the child's nutrition (qualitative and quantitative aspects), physical activity participation and screen time.

Written informed consent was obtained from the mothers at enrolment and at the age 5 health check. Ethical approval was granted by the Amsterdam Medical Center's Ethics Committee, and all procedures complied with the ethical standards of the Helsinki Declaration.[20]

Birth weight and infant growth

Birth weight and subsequent height and weight at 12 months of age were used in the analysis to reflect pre- and postnatal growth. Since most children had no measurements on exactly 12 months of age, weight and height were interpolated to this exact age using individual weight curves, based on prior growth data. The allowed age range for interpolation was 9-15 months. Birth height was largely missing in our dataset, and therefore not used in the analyses.

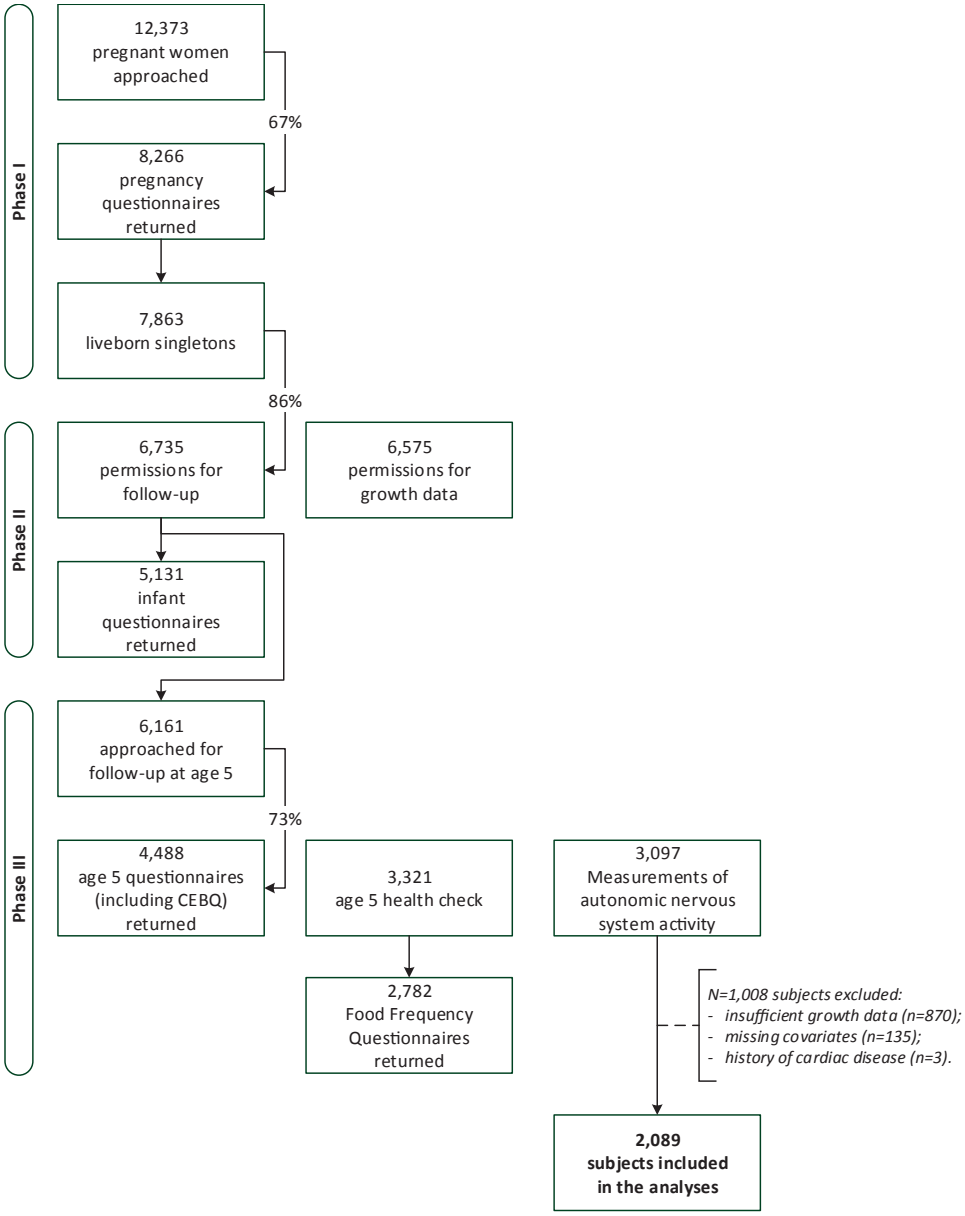

Figure 8.1 Flowchart of the sampling procedure of the ABCD study and the inclusion of the subjects in this study. Abbreviations: CEBQ - Child Eating Behavior Questionnaire.

Data on weight and height were standardized using internal sex-specific Z-scores, based on the weight and height distributions of the children in our cohort. Using these weight-for-age and height-for-age Z-scores, we derived conditional weight and conditional height. These conditional growth velocities are outcomes widely used to address the high correlation of weight with length, and of repeated measurements in the same individual over time. An overview of this approach has been presented in detail earlier[21], and specific to the ABCD study.[22] In summary, our conditional size measures were standardized residuals derived from regressing current size on all prior size measures. Conditional height was current height accounting for prior height and weight measures (but not current weight). Conditional weight was current weight accounting for current height and all prior weight and height measures. Conditional variables represent children's deviation from the expected size on the basis of their own previous measures and the growth of the other children in the study population, and can be interpreted as representing faster growth (positive conditional growth value) or slower growth (negative conditional growth value).

Autonomic nervous system activity

Cardiac pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA) are non-invasive measures of the sympathetic and parasympathetic nervous system control of the heart, respectively.[23]

The recording methodology of the PEP and RSA measurements has been described previously in detail.[24, 25] In summary, an electrocardiogram and impedance cardiogram were simultaneously recorded using the VU University Ambulatory Monitoring System. PEP is defined as the interval from the onset of left ventricular depolarization, reflected by the Q-wave onset in the electrocardiogram, to the opening of the aortic valve, reflected by the B-point in the impedance cardiogram signal. A lower PEP reflects an increase in contractility which is induced by increased sympathetic activity in humans.[26] RSA is the rhythmic fluctuation in heart rate that occurs during a breathing cycle, and is considered an index of parasympathetic activity, with higher RSA reflecting higher parasympathetic activity.[27] RSA is computed using the peak valley estimation, which is obtained automatically by subtracting the shortest interbeat interval during heart rate acceleration in the inspirational phase from the longest interbeat interval during deceleration in expiration.[28]

Energy intake and satiety response

Children's mean daily energy intake and eating behavior were assessed by the Food Frequency Questionnaire (FFQ) and Child Eating Behavior Questionnaire (CEBQ), respectively, completed by the mothers when the children were 5 years of age. Both

questionnaires are generally regarded as one of the most comprehensive instruments in assessing children's energy intake and eating behavior, and have been validated for use in Dutch school-aged children.[29, 30]

The FFQ approximates mean daily dietary intake based on reported consumption of 71 food items, with the previous four weeks as reference period.[31] For each food item parents indicated their child's habitual consumption in the reference period on a 6-point scale ranging from 'never' to '6–7 days a week'. The average daily intake of macro- and micronutrients was calculated by multiplying the reported daily intake of each food by its nutrient content, according to the Netherlands Food Composition Table NEVO 2001.[32]

The CEBQ is a questionnaire that measures eight dimensions of eating style in children, based on parents' reports of their child's usual behavior.[33] The 35 items are rated on a 5-point scale, ranging from 'never' to 'always'. For this study, the 'Satiety Response' dimension was used as the outcome measure, as this represents the ability of a child to reduce food intake to compensate for prior foods to regulate its energy intake, and thereby is of primary interest for this study. A lower score on this dimension reflects a lower satiety response and thus a more disadvantageous eating behavior. The Cronbach's alpha for this dimension was 0.80.

Physical activity and screen time

Physical activity level was based on mothers' responses to questions on duration of playing outside in summer and winter for weekdays and weekend days separately (0–5 hours/day) and sports participation (0–4 hours/ week). Responses to playing outside in summer and winter were averaged to compute hours/day playing outside. Mean duration of playing outside (0–5 hours/day) and mean duration of sports participation (0–4 hours/week) were summed to produce a mean duration of physical activity (hours/day), reflecting the child's usual physical activity level.

Screen time was based on mothers' report of the duration that their child spent watching TV or used a computer or console. Time spent watching TV and time using a computer or console were scored separately on a 7-point scale ranging from '(almost) never' to '5 hours/day or more' for weekdays and weekend days separately. Responses to each were recorded and summed to compute usual daily screen time.

Analysis plan

Descriptive statistics are given as means and SD for continuous data and as frequency distributions for categorical data, unless otherwise stated.

Primary analysis

For PEP and RSA, its association with birth weight Z-score, conditional weight gain and conditional height gain during infancy was assessed using multivariable linear regression analysis. Associations were adjusted for variables known to influence birth weight, infant growth or ANS activity, namely gestational age[23], sex[34], current age, height and BMI[34, 35], socioeconomic status[36], ethnicity[36], maternal pre-pregnancy BMI[37] and maternal smoking[38], alcohol intake[38], folic acid intake[39] and physical activity level during pregnancy.[40] Characteristics of these variables, including timing of measurement and method of categorization are presented in supplementary table S8.1. Both the unadjusted and fully adjusted associations are presented.

Model diagnostics and potential interaction

To evaluate the validity of the primary analyses' underlying statistical assumptions, we employed residual scatterplots of the associations. This potentially identifies outliers or a need for transformations or mixtures. Because of a potential U-shaped association of early growth with later disease risk[41], we assessed the presence of non-linear associations of birth weight, conditional weight or conditional height with either PEP or RSA by the significance of quadratic terms in polynomial regression analyses. As there are marked sex differences in the function of ANS[34], we explored effect modification by sex by alternately adding a sex × birth weight, sex × conditional weight and sex × conditional height interaction term. To account for potential ethnic-related differences in the association of early growth with ANS activity, moderation by ethnicity was evaluated by addition of nine interaction terms (birth weight, conditional weight and conditional height with Dutch, non-Caucasian and other-Caucasian descent).

Mediation analysis

A mediation analysis was conducted, guided by the mediation model represented in figure 8.2. The model uses birth weight, conditional height gain and conditional weight gain as independent variables, as defined earlier. Dependent variables are mean daily energy intake, satiety response, physical activity level and screen time. PEP and RSA are considered as potential mediators, and we present the mediating effects of both variables separately as well as the mediating effects of those combined. We used a procedure for the analysis, based on MacKinnon's multivariate extension of the product-of-coefficients strategy for models involving multiple mediators.[42] The set of covariates used to adjust the primary analysis (see Supplementary table S8.1) was also included in the mediation

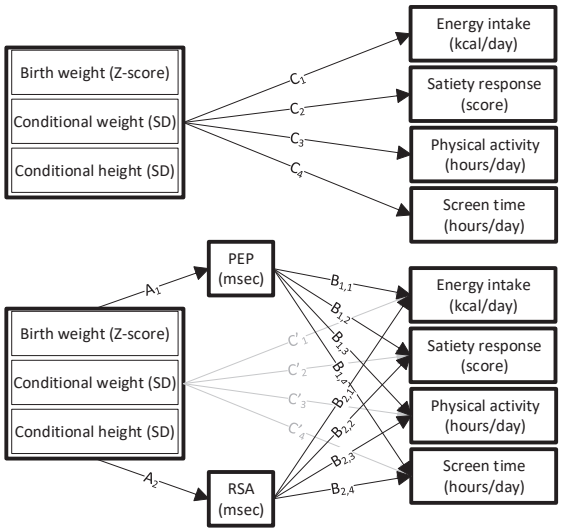

Figure 8.2. Graphical representation of the analysis model without (upper) and with (bottom) mediators, with the total (C), indirect (A×B) and direct (C′) paths.

model to control for exposure-outcome and exposure-mediator confounding. Statistical analyses were performed using SPSS Statistics for Windows, Version 22.0.

Sensitivity analysis for unmeasured mediator-outcome confounding

We assessed how the results obtained from the mediation analyses could be affected by possible unmeasured/residual mediator-outcome confounding, using a sensitivity analysis technique recently provided by Vanderweele. [43] The technique uses two parameters to quantify the amount of unmeasured confounding required to reduce the direct effect estimate to the null: γ_m, defined as the difference in means of the unmeasured confounder associated with a one unit difference in exposure (i.e., birth weight, conditional height gain or conditional weight gain), and δ_m, defined as the direct effect of the unmeasured confounder on the outcome variable (i.e., mean daily energy intake, satiety response, physical activity level or screen time), conditional on exposure, mediators and covariates. We assumed an unknown continuous confounder with a standard normal distribution with no exposure × unmeasured mediator-outcome confounder interaction.

RESULTS

Characteristics

Of the total ABCD cohort, 2092 children had complete growth data and ANS measurements available. Three children with a history of cardiac disease were excluded from further analysis, as this may greatly influence the ANS measurements, leaving 2089 children available for analyses (figure 8.1). Table 8.1 shows the demographic characteristics of the included children and the remainder of the cohort. Included children were more often of Dutch descent, had a higher socioeconomic status and higher birth weight, compared to the remainder of the cohort.

Association of birth weight, conditional weight and conditional height with PEP and RSA (A path)

Table 8.2 presents the results of the regression analyses of the association of birth weight, conditional weight gain during infancy and conditional height gain during infancy with PEP and RSA at age 5. All three growth parameters were positively associated with PEP, but not with RSA. Adjustment for confounding reduced the effect sizes, but the associations of birth weight and conditional height gain with PEP remained. The association of conditional weight gain with PEP, however, was greatly reduced due to strong attenuating effects of BMI and height on the association.

Model diagnostics and potential interaction

Visual evaluation of scatter diagrams and residual plots (not shown) suggested linear associations of birth weight, conditional weight and conditional height with PEP and RSA, without significant outliers or a need for transformation or mixture. There was no statistical evidence for a non-linear association of any of the growth variables with PEP or RSA in the polynomial regression analyses (P-value for the quadratic terms > 0.10). There were no interactions between birth weight, conditional weight gain and conditional height gain and sex. There was also no indication of moderation by ethnicity (all P-values for interaction >0.10). This indicates that the association of birth weight and conditional height gain during infancy with PEP is not sex-specific or limited to specific ethnic groups.

Association of PEP and RSA with energy intake, satiety response, physical activity level and screen time (B path)

Multivariable linear regression analyses revealed that neither PEP nor RSA was associated with energy balance-related behaviors, i.e. energy intake, satiety response, physical activity level and screen time, before and after adjustment for gestational age, sex, current age, height and BMI, socioeconomic status, ethnicity, maternal pre-pregnancy BMI, and maternal smoking, alcohol intake, folic acid intake and physical activity level during pregnancy. (See supplementary table S8.2)

Table 8.1 Characteristics of the participants of the study and remainder of the ABCD cohort.

	Included subjects	Remainder of the cohort
Perinatal characteristics		
Subjects with valid data (n)	2,089	4,486
Gender (% male)	51.4	49.2
Gestational age (weeks)	40.1 (1.2)	39.5 (2.1)
Parental SES (%)		
Low SES	13.8	21.3
Mid SES	27.3	29.3
High SES	58.9	49.5
Ethnicity (%)		
Dutch	77.6	57.3
Moroccan	4.6	7.9
Surinamese	2.5	6.0
Turkish	2.1	5.1
Other	13.3	23.7
Maternal pre-pregnancy BMI (kg/m^2)	22.9 (3.7)	23.2 (4.2)
Growth characteristics		
Birth weight (grams)	3550 (455)	3466 (486)
Birth weight (Z-score)	0.12 (0.99)	-0.25 (1.24)
Weight at 12 mo (SD)	0.01 (0.94)	0.00 (1.03)
Height at 12 mo (SD)	0.00 (0.95)	-0.05 (1.04)
BMI at 5 years (kg/m^2)	15.5 (1.5)	15.5 (1.6)
Height at 5 years (SD)	0.04 (0.99)	0.18 (1.10)
ANS variables		
Subjects with valid data (n)	2,089	1,008
Age at ANS measurement (years)	5.68 (0.48)	5.85 (0.54)
PEP (msec)	71.4 (9.2)	70.9 (8.9)
RSA (msec)	115.3 (55.0)	116.3 (54.8)
Questionnaire variables		
Subjects with valid data (n)	2,089	693
Energy intake (kcal/day)	1532 (338)	1552 (385)
Satiety response (score)	2.38 (0.49)	2.38 (0.51)
Physical activity (hours/day)	2.60 (1.19)	2.56 (1.22)
Screen time (hours/day)	1.38 (0.96)	1.55 (1.14)

Table 8.1 Descriptive statistics for the participants of the study and, when applicable, the remainder of the ABCD cohort. Data presented as means and SD in parenthesis unless otherwise stated. Abbreviations: BMI – Body Mass Index; SES – Socioeconomic Status; FFQ – Food Frequency Questionnaire; CEBQ – Child Eating Behavior Questionnaire.

Table 8.2 Associations of birth weight, conditional weight gain and conditional height gain with pre-ejection period and respiratory sinus arrhythmia.

	Pre-ejection period (msec)		Respiratory sinus arrhythmia (msec)	
	β (95%-CI)	P-value	β (95%-CI)	P-value
Birth weight				
Unadjusted	0.68 (0.29; 1.07)	<0.01	0.66 (-1.71; 3.03)	0.57
Fully adjusted (A path)	0.63 (0.13; 1.13)	0.01	1.51 (-3.13; 6.17)	0.52
Conditional weight 0–12mo				
Unadjusted	0.50 (0.11; 0.89)	0.01	0.82 (-1.56; 3.20)	0.59
Fully adjusted (A path)	0.59 (-0.28; 1.46)	0.18	0.38 (-3.47; 4.24)	0.85
Conditional height 0–12mo				
Unadjusted	0.94 (0.55; 1.34)	<0.01	2.22 (-0.16; 4.61)	0.07
Fully adjusted (A path)	1.06 (0.33; 1.79)	<0.01	3.24 (-0.94; 7.42)	0.40

Table 8.2 Associations (β-coefficients and 95% confidence intervals (95%-CI)) of birth weight, conditional weight gain and conditional height gain between 0 and 12 months with pre-ejection period and respiratory sinus arrhythmia (A path in figure 8.2). Given are both the unadjusted associations and fully adjusted associations, i.e., adjusted for gestational age, sex, current age, current height, current BMI, socioeconomic status, ethnicity, maternal pre-pregnancy BMI, and maternal smoking, alcohol intake, folic acid intake and physical activity level during pregnancy.

Mediation analysis

There was a positive association of conditional weight gain with screen time and an inverse association of conditional height gain with energy intake (table 8.3, total effect or C path) adjusted for gestational age, sex, current age, current height, current BMI, socioeconomic status, ethnicity, maternal pre-pregnancy BMI, and maternal smoking, alcohol intake, folic acid intake and physical activity level during pregnancy. The mediation analyses revealed that the mediation effects (table 8.3, indirect effects or A×B paths) were all very small. This holds true for the indirect effects of PEP and RSA separately, as well as for the combined indirect effect of PEP and RSA (ΣA×B path). This suggests that RSA and PEP are no important mediators in the association of birth weight, infant conditional weight and conditional height gain with energy intake, satiety response, physical activity level or screen time.

Sensitivity analysis for unmeasured mediator-outcome confounding

Supplementary table S8.3 shows the result of the bias sensitivity analysis, using the technique of Vanderweele.[43] The result represents the amount of unmeasured mediator-outcome confounding needed to reduce the two established direct effects of our mediation analyses (i.e., the direct effect of conditional height on mean daily energy intake and the direct effect of conditional weight on screen time) to the null.

Table 8.3 Mediating effects of PEP and RSA on the association of birth weight, conditional weight gain and conditional height gain with energy balance-related behaviors.

	Mean daily energy intake (kcal/day)	Satiety response (Score)	PA level (min/day)	Screen time (min/day)
Birth weight				
Total adjusted effect (C path)	10.06 (-9.00; 29.11)	0.002 (-0.039; 0.043)	2.90 (-3.74; 9.54)	-1.25 (-5.13; 2.63)
Total indirect effect (ΣA×B path)	0.21 (-1.30; 1.53)	-0.001 (-0.005; 0.004)	0.006 (-0.71; 0.74)	-0.23 (-0.80; 0.14)
Indirect effect through PEP (A_1×B_1 path)	0.10 (-1.27; 1.27)	-0.001 (-0.005; 0.002)	-0.004 (-0.57; 0.54)	-0.16 (-0.65; 0.15)
Indirect effect through RSA (A_2×B_2 path)	0.11 (-0.65; 0.97)	0.000 (-0.002; 0.004)	0.009 (-0.49; 0.48)	-0.07 (-0.47; 0.12)
Direct effect (C' path)	9.84 (-9.26; 28.95)	0.003 (-0.039; 0.044)	2.89 (-3.78; 9.56)	-1.02 (-4.91; 2.87)
Conditional weight 0–12mo				
Total adjusted effect (C path)	9.41 (-18.50; 37.31)	-0.040 (-0.085; 0.005)	0.59 (-6.58; 7.76)	4.36 (0.17; 8.56)*
Total indirect effect (ΣA×B path)	0.66 (-2.14; 3.87)	-0.001 (-0.006; 0.002)	-0.009 (-0.61; 0.59)	0.06 (0.36; 0.52)
Indirect effect through PEP (A_1×B_1 path)	1.10 (-0.86; 4.52)	-0.001 (-0.005; 0.002)	-0.003 (-0.54; 0.51)	0.11 (0.17; 0.57)
Indirect effect through RSA (A_2×B_2 path)	-0.44 (-2.80; 1.14)	-0.000 (-0.003; 0.002)	-0.006 (-0.39; 0.43)	-0.05 (-0.36; 0.14)
Direct effect (C' path)	8.75 (-19.24; 36.73)	-0.039 (-0.084; 0.006)	0.60 (-0.39; 0.43)	4.30 (0.10; 8.50)*
Conditional height 0–12mo				
Total adjusted effect (C path)	-17.97 (-34.06; -0.01)*	0.030 (-0.021; 0.080)	0.16 (-5.78; 6.09)	-3.08 (-6.54; 0.38
Total indirect effect (ΣA×B path)	1.31 (-2.19; 5.13)	-0.000 (-0.005; 0.004)	-0.02 (-0.91; 0.87)	0.14 (-0.39; 0.66)
Indirect effect through PEP (A_1×B_1 path)	1.83 (-1.21; 5.82)	0.000 (-0.003; 0.002)	-0.01 (-0.79; 0.86)	0.24 (-0.19; 0.81)
Indirect effect through RSA (A_2×B_2 path)	-0.52 (-2.87; 0.67)	-0.000 (-0.004; 0.002)	-0.02 (-0.74; 0.59)	-0.10 (-0.47; 0.11)
Direct effect (C' path)	-19.28 (-35.56; -3.00)*	0.030 (-0.021; 0.081)	0.18 (-5.81; 6.17)	-3.22 (-0.27; 6.71)

Table 8.3 Total effects (β-coefficients and 95% confidence intervals (95%-CI)) of birth weight, conditional weight gain and conditional height gain between birth and 12 months on the energy balance-related behaviors (C path in figure 8.2), total indirect effects of birth weight, conditional weight gain and conditional height gain on the energy balance-related behaviors through PEP and RSA (A×B path in figure 8.2) and the direct effects of birth weight, conditional weight gain and conditional height gain on the energy balance-related behaviors adjusted for PEP and RSA (C' path in figure 8.2). Analyses adjusted for gestational age, sex, current age, current height, current BMI, socioeconomic status, ethnicity, maternal pre-pregnancy BMI, and maternal smoking, alcohol intake, folic acid intake and physical activity level during pregnancy. * $P < 0.05$.

It indicates, for example, that if an SD increase of the unknown confounder is associated with 26 kcal/day less energy intake, it would require a 0.75 SD difference in means of the unknown confounder associated with one SD difference in conditional height to completely explain away the estimated direct effect. Although not entirely implausible, this may seem unlikely. In spite of the possibility of unmeasured mediator-outcome confounding, it seems that there is still evidence for an effect.

DISCUSSION

In this prospective cohort study, we assessed the independent associations of birth weight, conditional weight gain and conditional height gain between birth and 12 months with sympathetic and parasympathetic activity at 5 years of age. We found that both birth weight and conditional height gain were independently associated with PEP, but not with RSA. As a shorter PEP indicates higher cardiac SNS activity, this finding suggests that children with low birth weight have increased SNS activity compared to normal birth weight children, and that increased infant height gain was associated with decreased SNS activity. There was no association of birth weight, conditional height or conditional weight gain with RSA, indicating no shift in parasympathetic activity associated with birth weight or infant growth. There were no sex- or ethnic-related differences in our findings, so they hold true for both boys and girls of diverse ethnic groups. Sensitivity analyses indicate that it is unlikely that unmeasured mediator-outcome confounding explains the direct effects of our mediation model.

Manipulation of prenatal nutrition, due to uterine artery ligation[44] or maternal starvation[45], can profoundly influence SNS function in adult rats. Human studies also found direct associations of birth weight with indices of sympathetic function, including resting pulse rate and PEP, in healthy adults.[11, 12] The authors of these studies concluded that programmed sympathetic hyperactivity might be one mechanism linking low birth weight with increased blood pressure. This hypothesis is supported by a study in children, in which low birth weight was associated with raised arterial pressure and systemic vascular resistance, particularly following stress responses that predominantly involve sympathetic activation, in boys.[46] Girls with low birth weight showed no association of birth weight with blood pressure, but did show greater cardiac sympathetic activation at rest and during stress.[47]

Gademan *et al.* previously reported on the association of maternal prepregnancy BMI with their offspring's ANS activity in the ABCD cohort.[37] As a secondary finding, she found no association of birth weight with PEP. This in contrast to our study, where a positive association of birth weight with PEP is reported. This apparent inconsistency is attributable to differences in the standardization of birth weight. Gademan *et al.* used a gestational age-, parity- and sex-adjusted birth weight-score based on external references, while in this study we computed sex-specific internal Z-scores adjusted for gestational age and parity in our models. We chose this model to account for the interrelationships between birth weight, infant weight and infant height. Birth weight Z-score, conditional weight and conditional height are uncorrelated by design, and the use of Z-/SD-scores permit direct comparisons of the estimates. This model has the additional benefit that birth

weight Z-scores are normally distributed. Due to a more homogenous distribution of our internal birth weight Z-score, we were able to observe an association of birth weight with PEP that was left undetected by Gademan *et al*.[37]

In addition to the positive association of birth weight with PEP, we found infant height gain to be positively associated with PEP as well, implying an inverse association of infant height gain with SNS activity. Relatively little is known about the relationship of postnatal growth with ANS activity. To our knowledge, the only available human data involves Jamaican children, in which faltering height was associated with higher heart rates during stress, indicating higher sympathetic activity.[48] This mirrors the finding in our study. This inverse association of infant height gain with sympathetic activity is also in line with other studies showing beneficial effects of increased height gain, including a more favorable body composition characterized by an increase in fat-free mass[49, 50], and a decreased CVD risk.[51]

Strengths and limitations

To the best of our knowledge, this is the first study to assess the independent associations of birth weight, postnatal weight gain and postnatal height gain with ANS activity, and the mediating effects of ANS in the association of perinatal growth with energy balance-related behaviors. That this study prospectively assessed birth weight, infant growth patterns, ANS properties and energy balance-related behaviors in a large population-based cohort adds to its strength.

There are several limitations that need to be addressed in future work. First, we only included children of the ABCD cohort with valid ANS measurements, complete growth data and no history of cardiac disease. This reduced the number of eligible children to 2089, yet increased the accuracy of the data analyzed. Because participation rates were higher among children from higher socioeconomic groups and of Dutch descent, these children were overrepresented in our analysis. Thus a risk of non-response bias is acknowledged. In addition, children with low birth weight were relatively underrepresented in our sample, which reduced our power to detect effects.

Second, because of the observational nature of the study, with ANS activity and behaviors both measured at 5-6 years, we could not infer causality. Because PEP and RSA show substantial stability over childhood years[28, 52, 53], we used PEP and RSA as a reflection of ANS activity in the previous period, and hypothesized that this might influence behavior at age 5-6. However, research in adults has also suggested reversed causality, i.e., that levels of physical activity or diet influence ANS activity.[54, 55] So it cannot be excluded that energy balance-related behaviors through early childhood influence ANS at age 5-6.

But regardless of the direction of the causal vectors, neither PEP nor RSA was associated with the energy balance-related behaviors, so these associations cannot explain some of the changes in behavior associated with early growth.

Third, the energy balance-related behaviors were assessed by parent report. Although parent report is widely used to assess behaviors in younger children, there is concern about the validity of their estimates. The questions related to physical activity and screen time have never been validated for use in preschool children, and these questions are subject to recall and social desirability bias. This may be an explanation for the relatively low reported screen time and high reported physical activity level in our cohort.

In summary, birth weight and infant height gain were both inversely associated with SNS activity in our sample of 5-year old children. These results add to the known detrimental effects of low birth weight and beneficial effects of infant height gain. SNS activity, however, did not mediate the associations of suboptimal infant growth with detrimental energy balance-related behaviors. As individual differences in ANS activity predict increased risk of hypertension and CVD, these differences may offer insight into the early life origins of these chronic diseases and provide further basis for public health strategies. If the processes producing susceptibility to hypertension and CVD are established in early life, then this might be the period at which CVD risk is most sensitive to public health strategies to reduce it.

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9. GENERAL DISCUSSION

INTRODUCTION

The aim of the present thesis was to elucidate the role of prenatal and early postnatal growth, as measured by birth weight and infant growth, respectively, in (i) childhood energy balance-related behaviors, i.e. physical activity (PA), sedentary behavior (SB), energy intake and satiety response, (ii) physical fitness and (iii) autonomic nervous system (ANS) activity. The studies of this thesis were embedded in the Amsterdam Born Children and their Development (ABCD) study, a prospective community-based cohort study initiated in 2003 by the Municipal Health Service, the Academic Medical Center and the VU University Medical Center. One of the objectives of the ABCD study is to gain more insight into early life conditions and the extent to which these conditions explain children's health in later life.[1]

The results of the studies presented in this thesis generally indicate that differences in energy balance-related behaviors, physical fitness and ANS activity in childhood are in part explained by differences in prenatal and early postnatal growth. Because of the strong health effects associated with energy balance-related behaviors, physical fitness and ANS activity, these results point to a potential underlying mechanism linking suboptimal prenatal and early postnatal growth to a higher risk of obesity and cardiovascular disease in later life.

In this chapter, we reflect on the main findings of this thesis, discuss the broader perspective and potential clinical relevance of our results, evaluate the clinical and methodological limitations of our studies, and consider the implications of our findings for public health policies. Finally, we propose directions for future research on the Developmental Origins of Energy Balance-Related Behavior and Physical Fitness.

REFLECTION ON THE MAIN FINDINGS

Obesity and cardiovascular disease are considered the biggest threats to global health of the 21st century.[2, 3] A substantial body of epidemiological evidence now suggests that suboptimal prenatal and early postnatal growth caused by an unbalanced maternal diet, placental insufficiency or postnatal nutritional excesses may elicit susceptibility to the development of later obesity and cardiovascular disease. In search of the underlying mechanisms, a concept that is central to this thesis emerged, i.e., that the processes we appreciate to underlie the association of early growth with later disease may encompass adaptations in energy balance-related behaviors and physical fitness levels. Supporting animal data for this hypothesis comes from several rat models in which unbalanced

early life nutrition was shown to affect appetite and voluntary exercise capacity.[4-9] However, based on a systematic review of the literature, there is no evidence to support the hypothesis that birth weight (as a proxy for prenatal nutrition) is associated with any of the energy balance-related behaviors, i.e., PA, SB, energy intake or eating behavior, in the human population.(**Chapter 4**) This finding is substantiated by our study, where gestational age-adjusted birth weight was neither significantly associated with energy intake or satiety response at 5-6 years of age in the full ABCD cohort (**Chapter 5**), nor significantly associated with objectively-assessed PA or SB in an add-on study population of almost 200 children at age 8-9 years.(**Chapter 6**)

There are several explanations for the contradictory findings between animal models and human epidemiological studies, including ours. First, there is a marked difference in timing in the development of energy-balance regulation between species. In rodents, the hypothalamus is structurally and functionally immature at birth, and many developmental events that occur in the early postnatal period in rats take place in the third trimester of human pregnancy.[10] Second, the perinatal environment is markedly different, due to the large litter sizes of rodents compared to usual singleton pregnancies in humans and differences in intrauterine endocrine stimuli. Third, locomotor activity and feeding behavior of rats are significantly altered by chronic stress, so differences in these behaviors may be interpreted to reflect a stress response, rather than an altered energy balance regulation.[11, 12] Fourth, many of the nutritional regimens used to model early life malnutrition in rodent models are rather extreme, with maternal intake during gestation reduced to 30% of controls.[5] This might induce a teratogenic effect with pathological responses not directly relevant to the normal human pregnancy. Therefore, caution is needed when extrapolating findings from these rat studies to the human situation.

Postnatal growth

It has only relatively recently been realized that the window of developmental plasticity extends into postnatal life.[13] For example, crossing of two growth lines on a standard infant weight chart in the first six months of life is associated with obesity five to ten years later.[14] Moreover, it has been argued that it is growth in infancy rather than the fetal environment that induces obesity[15, 16], metabolic abnormalities[17] and cardiovascular dysfunction.[18] Yet, the association of infant growth with later physical fitness or energy balance-related behaviors is relatively understudied. Our systematic review of the literature and best-evidence synthesis revealed that there is currently insufficient human evidence to address the association of infant growth with energy balance-related behavior, and we concluded that further original research is required on this topic.(**Chapter 4**) In this thesis, we aimed to partly fill this gap by reporting the associations of several indices of infant growth (e.g., growth in weight, height or BMI) with aspects of energy balance-related behavior

(i.e., PA, SB, energy intake and satiety response) within the ABCD cohort. We found that accelerated infant weight gain was associated with increased energy intake and diminished satiety response at age 5 (**Chapter 5**) and increased SB at age 8-9 years.(**Chapter 6**) Accelerated height gain in infancy was associated with diminished energy intake at 5 years of age (**Chapter 5**) and higher moderate-to-vigorous PA levels at age 8-9.(**Chapter 6**) Similar to infant weight gain, accelerated infant BMI gain was associated with increased childhood SB (**Chapter 6**), but also with diminished neuromuscular fitness at age 8-9. (**Chapter 7**) The results of these studies produce a converging conclusion, i.e., that it is not the prenatal but the postnatal growth trajectory that is associated with energy balance-related behaviors and physical fitness levels in children.

Our findings further underscore the importance of the definition of postnatal growth, because, as noted above, the associations with the different outcomes vary greatly between weight gain and linear growth in infancy. In the literature, the effects of both infant weight and height gain on markers of cardiovascular health have been the subject of investigation, often related to additional factors such as the gender of the child, preceding prenatal growth and the timing and severity of the weight or height gain, leading to a complex picture. These studies indicate that children with accelerated weight gain during infancy are at greatest risk of childhood and adolescent obesity[15, 16, 19] and of childhood cardiovascular dysfunction[18], while accelerated height gain is associated with a more healthy body composition characterized by an increase in fat-free mass[20] and a lower cardiovascular disease risk.[21] Although infant weight gain has been associated with an increase in lean mass as well.[20] In general, this concurs with the detrimental weight gain and beneficial height gain effects observed in our studies.

A pitfall of several studies assessing the potential unfavorable effects of accelerated weight gain is that they focus on these effects in isolation, while the most accelerated growth trajectories follow impaired fetal growth, the so called 'catch-up growth'.[15, 22] Rather, the issue is whether the effects of excessive postnatal weight gain are amplified when they follow fetal growth restriction, i.e., when a 'mismatch' between prenatally anticipated and postnatally experienced nutrition is likely to occur. This 'match-mismatch concept' was noted by Eriksson *et al.,* who found the highest risk of adult-onset disease in subjects of lower birth size, who as children experienced rapid weight gain.[23, 24] This association suggested an interaction between prenatal and postnatal nutritional cues, and an increase in disease susceptibility, especially if the prenatal environment differs from the subsequent postnatal situation. This concept has also been observed in risk of obesity[22] and type 2 diabetes.[25] Our results indicate the same 'mismatch concept' could be applied to physical fitness, as the lowest aerobic fitness levels were observed in children who showed accelerated infant weight gain following low birth weight.(**Chapter 7**)

This synergistic effect was not present for the other variables of interest in this thesis, so the exact implication of this one 'mismatch effect' to the spectrum of development of energy balance-related behaviors and physical fitness is a matter yet to be resolved.

Childhood growth

The period of time after birth in which nutrition may induce conditioning effects in humans remains to be substantiated, with some studies highlighting the immediate postnatal period[26] and others indicating that this period may extend well into childhood.[27] In **Chapter 5**, the size of the study cohort and the expression of growth as conditional height and weight gain enabled us to directly compare the relative contributions of different postnatal growth periods on energy intake and satiety response. This study revealed that the associations of childhood weight gain with later energy intake and satiety response appeared to be three times that of weight gain in early infancy (i.e., between birth and six months). This mirrors the findings of other studies addressing the effects of different postnatal growth periods on body composition, which showed that childhood weight gain was more strongly related to central fat accumulation than infant weight gain.[28, 29] This might suggest that childhood is a more important period in the establishment of energy balance than infancy. Unfortunately, this hypothesis could not be tested with regard to PA, SB or physical fitness, due to the limited sample size of the add-on study population at age 8-9 years and the design of the studies addressing PS, SB and fitness.

An underlying mechanism: the autonomic nervous system?

The behaviors assessed in this thesis are a reflection of central nervous system orchestrated processes. In this context, a potential pathway may find its origin in early life influences on ANS activity. Altered behavior, appetite and satiety responsiveness have been repeatedly associated with variations in ANS function[30], ANS activity is consistently linked to later obesity and cardiovascular disease[31] and there is convincing prospective evidence that indicators of early life nutrition, including birth weight and maternal prepregnancy BMI, explain a large proportion of later autonomic activity.[32, 33]

In **Chapter 8**, we focused on ANS activity as a potential mechanism explaining the association of early growth with energy balance-related behaviors, as established in the prior chapters. Here, we showed that birth weight and infant height gain were inversely associated with childhood sympathetic activity, but that these associations did not mediate any of the associations of birth weight or infant growth with the energy balance-related behaviors. This indicates that perinatal growth could impact the development of the ANS, but that the implications of these influences on later disease risk should be sought outside behavioral processes. The sympathetic nervous system is integral to obesity through its interrelationships with leptin homeostasis and basal metabolic rate.[34]

It is pertinent to complications of diabetes and cardiovascular disease through its efferent effects on the heart and peripheral vasculature.[35] It contributes to hypertension and renal dysfunction through its effects on salt retention and glomerular filtration.[36] As such, higher sympathetic activity may play an important part in the causation of obesity, hypertension and type 2 diabetes in subjects with impaired fetal or infant growth rates.

In summary

In summary, the Developmental Origins of Energy Balance-Related Behaviors and Physical Fitness are characterized by an independent effect of increased infant weight gain on increased childhood energy intake and SB and decreased satiety response, an independent effect of increased infant height gain on increased childhood energy intake and PA, a synergistic effect of low birth weight and increased infant weight gain on decreased aerobic fitness and an independent effect of increased childhood weight gain on increased energy intake and decreased satiety response. Both birth weight and infant height gain were inversely associated with sympathetic activity at age 5-6, but this did not explain the associations of birth weight and infant growth with energy balance-related behaviors. These associations, and their hypothesized role in the Developmental Origins of obesity and cardiovascular disease, are schematically represented in figure 9.1.

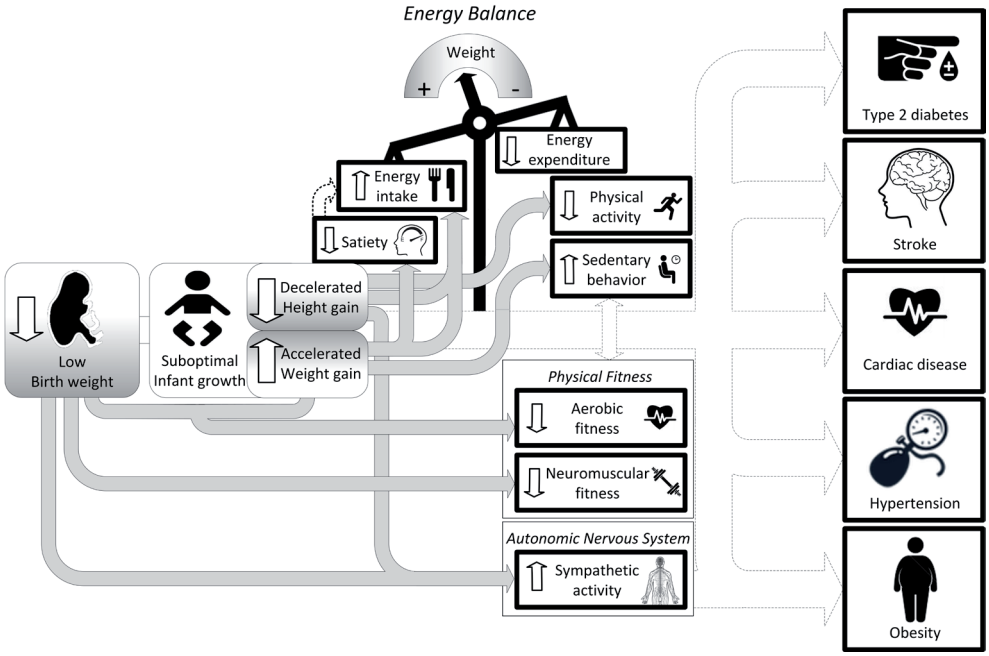

Figure 9.1 Graphical representations of the main associations as observed in this thesis (gray arrows) and their hypothesized role in the Developmental Origins of obesity and cardiovascular disease (white arrows).

BROADER PERSPECTIVE AND POTENTIAL CLINICAL RELEVANCE OF THE FINDINGS

How relevant are the effect sizes associated with early life growth?

In **Chapter 5**, we found that every Z-score gain in conditional weight between the first and third month of life was associated with an extra mean (±SD) daily energy intake of 29.7 (±12.8) kilocalories (kcal) at age 5-6 years. In contrast, every Z-score conditional height gain in this period led on average to the consummation of 35.1 (±11.9) less kcal per day at age 5-6. On the expenditure arm of the energy balance, we found that each SD weight gain in infancy was associated with 11.5 minutes more sedentary time per day, corresponding to 10 kcal less energy expenditure per day if the sedentary time replaced low-intensity PA.[37] We also observed a 2.8 (±1.3) min/day increase in moderate-to-vigorous PA for every SD height gain in infancy, which equals to 5-10 expended kcal. How should this relative difference in energy intake and expenditure be assessed, and how large is the effect on later weight compared with the needed effect for reversal of the current obesity pandemic?

The effect needed depends on the target. The obesity target of the WHO's Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020, adopted at the World Health Assembly in 2013, appears modest, setting a target of no increase in prevalence of obesity between 2010 and 2025. This, however, does not aim to reverse the obesity pandemic, only halting it. The estimated reduction in energy gap needed to achieve this goal is, on average, 41 kcal/day per child, which is easily achieved by the optimization of infant growth.[38] An ambitious target would be a reduction of weight from present levels to the levels seen in children a generation or more ago, and for this change some relatively simple calculations can be made. Comparison of children in the Netherlands in the 1980s[39] with those of children in the most recent Dutch survey[40] show an increase in body weight of about three kilograms in children aged 5-8 years, which corresponds to an increase in overweight and obesity prevalence from 5 to 11%.

Hall *et al*. has achieved substantial progress in quantifying energy balance and body weight dynamics in adults, and this work has been used to predict bodyweight and body composition dynamics resulting from interventions in adult populations.[41] The development of similar quantitative models of bodyweight dynamics in childhood is complicated by the processes of growth and development. A model that includes growth and development has been published by Hall and colleagues, and can be used to calculate the energy balance dynamics in children.[42] Their formulae can be used to estimate the energy intake change that would lead to a relative change in weight at various ages:

Boys (7–18 y): daily kcal per kg=68 – 2.5 × Age in years,

Girls (7–18 y): daily kcal per kg=62 – 2.2 × Age in years.

From these formulae, a change in relative weight of three kg for an 8-year-old child can be estimated to result from decreasing the energy intake by around 130-145 kcal per day. Half of this ambitious target could be attained by preventing a Z- or SD-score increase in weight in early infancy and promoting a gain in height Z-score instead, leading to a decrease in energy gap of 80 kcal/day, which amounts to a weight reduction of more than 1.5 kg.

However, this perspective on the effects of early life growth on the development of obesity is based on a simplistic 'energy in' vs. 'energy out' dichotomy, whilst obesity is acknowledged as a far more complex issue.[43] The behaviors operating in the energy balance interact and effects on one energy balance-related behavior can be compensated for by another. This explains why some apparently straightforward interventions do not achieve the desired result, as noted for initiatives targeting energy intake or physical activity levels to achieve weight loss.[44] This also makes the calculated effects of optimizing growth on the alteration of energy balance-related behaviors, and thereby on obesity risk, theoretical. Practice will undoubtedly prove to be more intractable.

Tracking of behaviors

Part of the rationale of our focus on the determinants of childhood energy balance-related behavior is the presumption that these early life behaviors, once developed, will carry over into later life. It is often assumed that this link exists, but there is only modest evidence to support the persistence of behavior.[45] This behavioral persistence over time is known as 'tracking' and relates to the maintenance of a rank-order position compared to other subjects. A main consideration, therefore, might be whether early growth-induced susceptibility to low PA levels, increased SB and increased energy intake in childhood lead to less PA participation, more sedentary time and more energy intake in adulthood, with subsequent elevated risk of adult disease.

Levels of tracking through various stages of the lifespan have been reviewed for SB and PA.[45, 46] SB tracks with moderate to strong stability from mid-childhood to adolescence, from adolescence to adulthood and across various ages during adulthood.[45] PA appears to track less consistently in childhood as a systematic review found that 64% of studies on the tracking of PA in childhood reported moderate to strong tracking as opposed to 83% of studies on tracking of SB.[46] Tracking of PA was especially low across transitional phases, such as from childhood to adolescence or from adolescence to adulthood.[47] The

authors concluded that substantial tracking might only be relevant for SB, not for PA, as PA is apparently more influenced by day-to-day patterns, seasons, and various life events. Examples of such life events include changing schools, school-to-work transition, leaving home, moving house, moving to a new neighborhood, and biological and psychological development (especially puberty and adolescence). Any one of these can significantly affect activity habits, and therefore it is to be expected that activity levels will fluctuate greatly within any one individual over all stages of the lifespan.[47]

A 2012 review of tracking of childhood energy intake found evidence to suggest that there is moderate tracking of energy intake, macronutrients and certain dietary products in childhood and from childhood to adolescence.[48] More recent data from the ALSPAC cohort supported this conclusion, by showing moderate tracking of dietary patterns and energy intake from ages 7 years to 10 years to 13 years[49], and a German birth cohort study additionally showed fair tracking of a broad range of food items and macronutrients during the transition into adolescence.[50]

In conclusion, although there is only moderate evidence to suggest that energy balance-related behaviors track from childhood to adulthood, it seems plausible that children with high early growth-induced SB and increased energy intake are more likely to be an adult with high SB and energy intake. Large observational studies suggest that dose-response relationships exist of PA, SB and dietary intake with cardiovascular disease and all-cause mortality, so even moderate tracking of these behaviors may be noteworthy because of the effects they exert on later health and well-being.[51, 52]

CLINICAL CONSIDERATIONS

Postnatal weight gain: cause or effect?

How long after birth conditioning effects can be induced in children is an open question, but it is clear that they can persist through infancy. It has been argued that childhood weight gain, more than weight gain in infancy, induces metabolic conditioning.[25] Indeed, in **Chapter 5** we directly compared the effects of infant weight gain with childhood weight gain on later energy intake and satiety response, and for both outcome variables the association with childhood weight gain was three times as large as the association with infant weight gain. This suggests that childhood might be a more important period for the long-term setting of energy balance-related behavior than infancy.

However, when assessing the effects of weight gain on energy balance-related behavior in a period in close proximity to the period in which these effects are observed, it is difficult

to judge cause and effect. More specifically, although the temporal order of our findings suggest an effect of weight gain between 1 and 5 year on energy intake and satiety response at age 5-6, it cannot be excluded that some children already had an increased energy intake and diminished satiety response at age 1, contributing to excessive weight gain between age 1 and 5 years. This issue is equally relevant for the observed association of infant weight gain and childhood SB, described in **Chapter 6**. If the children showing increased SB at age 8-9 years already were relatively sedentary at a very early age, this could have contributed to, instead of being the consequence of, increased weight gain in infancy.

The hypothesis that detrimental energy balance-related behaviors led to infant and childhood weight gain, might also explain why the magnitude of the association of childhood weight gain with energy intake and satiety response are so much larger than the association of infant weight gain. This is an example of Peto's "horse racing principle"[53], where childhood is a horse race and race position corresponds to the energy balance-related behavior, with weight gain at a specific time point being a proxy for the energy balance-related behaviors in the preceding period. In a race, horses near the front of the field and/or overtaking others have a better chance of winning. This explains why childhood weight gain, reflecting detrimental energy balance-related behavior at age 1-5 years, has more effect on later energy balance-related behavior than infant weight gain. The horse's position near the end of the race is more relevant for the finishing position than its position earlier in the race. However, infant weight gain still has substantial predictive value, independent of childhood weight gain. Using the racing analogy again, the leading horses at any point in the race have run the fastest to that point and are likely to continue running fast and/or hold the front position.

The key issue concerning the interpretation of the association is causality, which cannot be inferred from epidemiological and observational studies. The classical method of assessing causality has been developed by Bradford Hill in 1965.[54] He proposed that an association should meet a set of criteria in order to infer causality. One important criterion is that the evidence shows that experimental manipulation of the exposure leads to change in the outcome. This reveals a situation difficult to overcome. A reasonable alternative is for studies to focus on how and when energy balance-related behaviors diverge between accelerated weight gain subjects and their normal weight gain peers. Thus, future studies should assess these behaviors from a very early age onwards.

What do we measure when we measure growth?

Throughout this thesis, considerable attention is given to birth weight as a proxy of prenatal growth as a proxy of the prenatal nutritional environment experienced by the fetus. It is important to consider that birth weight is a crude measure of prenatal nutrition. Clinical observations recognize that long-term consequences for the fetus' health can occur after nutritional insults in the absence of reduced birth weight. For example, exposure to the Dutch famine (1944-1945) in the first trimester was shown to increase the chance of coronary heart disease without effects on birth weight.[55] More recently, impaired first trimester fetal growth was associated with an adverse cardiovascular risk profile independent of birth weight in a cohort of school-aged children.[56] Similarly, low birth weight could be the result of multiple fetal influences: a low birth weight fetus at term may result from a slow growth trajectory throughout gestation, a rapid trajectory followed by a period of greater constraint, or simply reflect mild prematurity. It is likely that the longer-term consequences of these developmental trajectories may vary. Birth weight is thus a very low-resolution marker, not necessarily lying on the causal pathway to disease.

Even though measurement of the trajectory of fetal growth throughout gestation is feasible, it is not routinely undertaken. Postnatal growth is, however, routinely measured in the Netherlands. This allows detailed growth to be used as a biomarker of later risk. The problem with the use of such measures is that, as with birth weight, growth trajectory is more a measure of the integrated responses of the infant to a complex set of environmental circumstances. It is an end result of effects on metabolism, appetite, immune function, emotional stimuli, and other influences such as parental bonding, sedentary behavior, etc. So, again, infants with similar growth trajectories can have different combinations of these processes in operation and so different later disease risk.

The broader question concerns the nature of any biomarker. Is it a component of a mechanistic pathway from prenatal cues to a postnatal phenotype, or rather a measure of an epiphenomenon that has occurred in parallel? Very often the answer to this question is unknown. Surrogate or proxy biomarkers for a process are not necessarily inferior if the effects on them are large and consistent, for example, the use of cholesterol as a marker of cardiovascular disease risk.[57] Epigenetic studies may prove to be valuable on this point.

Epigenetics: new opportunities?

Developmental epigenetics, which is the study of the external influences modifying the level of expression of genes, may provide new opportunities to measure the influence of early life nutrition to disease risk. For example, the degree of methylation of one CpG associated with the RXRA gene is related both to aspects of maternal diet in early

pregnancy and to child's fat mass 6–9 yr later.[58] In this example, the effect size is large, with the level of methylation accounting for 25% or more of the variation in fat mass of the child. This is larger than any other early life marker of lean or fat mass or current estimates of the fixed genomic contribution to obesity. Confirmation of this concept has come from the work of others using cord blood samples[59, 60] and for the Southampton cohort with child's bone density as an outcome.[61] These epigenetic studies have expanded enormously in recent years. Changes in the fetal epigenome are now being studied systematically in relation to maternal and environmental factors as well as major health-related endpoints such as cardiovascular mortality.[62] These studies offer promise that, with the use of epigenetic marks as biomarkers of early life exposure, nutritional effects on development may be more adequately addressed in future research.

METHODOLOGICAL CONSIDERATIONS

The ABCD study has its methodological strengths and limitations, as does any epidemiologic study. The methodological considerations directly relevant to the specific studies have been discussed in the Discussion sections of the previous chapters. In this section, we will address two issues of general importance: (1) the definition of growth, and (2) selective nonresponse.

The definition of growth

Throughout this thesis, we used different expressions of birth weight and infant weight gain as indicators of prenatal and postnatal growth, respectively. In **Chapter 5 and 8**, we relate individual growth trajectories to the mean growth values of the total ABCD cohort, using internal Z-scores in a conditional growth model. In **Chapter 6 and 7**, we take a population-average approach, by expressing birth weight and infant growth as a standard deviation score, based on national reference curves of the Netherlands Perinatal Registry and The Netherlands Organization for Applied Scientific Research, respectively. What are the potential consequences of these different approaches? And, since a critical review of the statistical approaches to modeling growth pointed out that detected effects of growth are highly dependent on the model used[63], would a different approach have yielded different results?

The conditional growth model used for the analysis of data of the full ABCD cohort (**Chapter 5 and 8**) defines conditional growth as the difference between observed and predicted body size, with body size expressed as a sex-specific internal Z-score. The predicted body size measured on time *t* is obtained by regressing the observed body size on all preceding body sizes since birth (and, potentially, other covariates), with

conditional growth being the residual error of the regression analysis. As the residual error term is uncorrelated to covariates in the model by definition, this ensures that conditional body size on any occasion is uncorrelated to all preceding body sizes and all preceding conditional body sizes. Another main advantage is that the use of conditional growth permits direct comparison of estimates across the different infant and childhood growth periods. The interpretation of the regression coefficient is methodologically uniform but not very intuitive: it represents the expected change in outcome given one unit difference between observed body size and expected size based on prior individual growth and the mean growth of the ABCD cohort.[64]

The population-average approach used for the analysis of data from the add-on study of PA, SB and fitness (**Chapter 6 and 7**) is relatively straight-forward: the presented values of birth weight and infant growth relate to the sex-, parity- and gestational age-adjusted average and distribution of the weight and height of Dutch children. The resulting SD score is then regressed on the outcome through a linear regression analysis. However simple and straight-forward, the weight distribution of the total ABCD cohort is slightly negatively skewed, thereby limiting the discriminating power of this model compared to the conditional growth model. In addition, a potential difficulty in the interpretation of the population-average SD scores arises due to collinearity among the series of body size measurements. As growth is a continuous process, successive body size measurements are highly correlated, and the shorter the age interval between two measurements the greater the correlation. For example, the correlation coefficient for birth weight SD and difference in weight SD between birth and 12 months in our add-on study population of 194 children is -0.70. This problem is overcome by adjusting the analysis of birth weight for infant growth in the primary model, and vice versa, enabling us to evaluate the independent effect of both variables.

Our choice of methodological approach was depended on the study design (e.g., whether we studied the effects of only one postnatal growth period or several independent postnatal periods) and the study population (e.g., the full ABCD cohort or a subsample). In the analyses with a limited number of determinants and a relatively small sample size, the population-average approach was sufficient. When multiple growth variables were compared and the study sample represented the total ABCD cohort, we adopted the conditional growth model. To aid the comparison of these approaches, and to ascertain that the choice of the model did not influence our main conclusions, we reran the analyses off all the prior chapters of this thesis, uniformly first using a conditional growth model, with infant growth defined as conditional weight change between birth and 12 months, and second by the population-average approach. The results of these analyses are presented in table 9.1.

Table 9.1 Comparison of the results of the prior chapters using different statistical models

Chapter	n	Outcome	Conditional growth model		Population-average approach	
			Birth weight (Internal Z-score)	Infant weight gain (Conditional weight gain 0-12months)	Birth weight (adjusted SD score)	Infant weight gain (ΔSDS 0-12 months)
5	2,227	Energy intake (kcal/day)	-7.1 (-30.9; 16.7)	16.9 (5.1; 28.7)*	-8.7 (-34.4; 17.0)	11.0 (2.37; 19.7)*
		Satiety response (score)	-0.01 (-0.04; 0.02)	-0.05 (-0.09; -0.01)*	-0.01 (-0.05; 0.02)	-0.03 (-0.10; 0.03)
6	183	Physical activity (min/day)	-0.7 (-3.5; 2.1)	1.3 (-1.7; 4.3)	-0.2 (-3.2; 2.8)	0.5 (-2.4; 3.5)
		Sedentary behavior (min/day)	7.1 (-0.2; 14.4)	14.6 (5.1; 24.0)*	8.5 (-1.5; 18.5)	10.2 (1.3; 19.1)*
7	194	Aerobic Fitness (20-m MSRT stage)	0.31 (0.02; 0.60)*	-0.22 (-0.58; 0.15)	0.19 (-0.16; 0.54)	-0.16 (-0.52; 0.21)
		Neuromuscular fitness (hand grip strength, kg)	0.40 (-0.10; 0.90)	-0.06 (-0.69; 0.58)	0.34 (-0.26; 0.93)	-0.08 (-0.69; 0.54)
		Neuromuscular fitness (SBJ, cm)	1.55 (-1.32; 4.42)	-1.32 (-4.94; 2.30)	2.44 (-0.77; 5.66)	-0.74 (-4.08; 2.60)
8	2,089	SNS (PEP, msec)	0.63 (0.14; 1.11)*	1.34 (-1.65; 4.33)	0.41 (-0.05; 0.87)	1.07 (-0.36; 2.49)
		PNS (RSA, msec)	0.25 (-0.27; 0.76)	0.42 (-2.74; 3.60)	0.21 (-0.52; 0.94)	0.50 (-2.35; 3.34)

Table 9.1 Comparison of the results of the main analyses of the prior chapters using both a conditional growth model (with birth weight and weight at 12 months expressed as internal Z-scores and using conditional growth parameters, left columns) and a population-average approach (with birth weight and weight at 12 months expressed as sex-, parity- and gestational age-adjusted SD score, right columns). Presented are the fully-adjusted models, adjusted for the same set of confounding variables as in the corresponding chapters. Abbreviations: kcal – kilocalories; 20-m MSRT – 20-meter multi-stage shuttle run test; SBJ – Standing Broad Jump; SNS – Sympathetic nervous system; PEP – Pre-ejection period; PNS – Parasympathetic nervous system; RSA – Respiratory sinus arrhythmia.

Rather reassuringly, when comparing the main outcomes of the two approaches, the magnitude of the regression coefficients and level of significance were in general similar. As noted above, the conditional growth model has the power to detect small associations that remain non-significant by the population-based approach. This is apparent for the association of birth weight both with aerobic fitness and with sympathetic activity. The conditional growth model revealed a small but significant association of Z-score birth weight with attained stage on the 20 meter multistage shuttle run test (β: 0.31. 95%-CI: 0.02; 0.60. $P < 0.05$), while the population-based approach failed to detect a significant association. The latter association was presented in the original article (**Chapter 7**). For sympathetic activity, its association with birth weight was apparent with the conditional growth model, with an 0.63 msec increase in cardiac pre-ejection period for every Z-score increase in birth weight (95%-CI: 0.14; 1.11, $P = 0.03$), equal to the results described in the respective chapter (**Chapter 8**). However, this association of birth weight with sympathetic activity failed to reach significance with the population-based approach (β: 0.41 msec/Z-score. 95%-CI: -0.05; 0.87. $P = 0.07$).

In conclusion, each of the approaches used in this thesis has their advantages and limitations and its choice depended on the respective hypotheses, study design and sample size. Interpretation of the data should be done with respect to the model used. Re-analyses of our results show that certain choices in methodology produce similar results, but may flip individual P values in the near- of just-significant region to the other side of the (artificial) P=0.05 divide.

Selective nonresponse

In phase I of the ABCD study, the overall response rate was 67%, and in phase III the response rate was 73%. This agrees with the participation rates observed in other large-scale community-based pregnancy cohorts, such as the Generation R study in the Netherlands (61%)[65] and the ALSPAC study in the United Kingdom (85%).[66] For the add-on study, we selected 400 children from the original cohort with complete data and Dutch ethnicity. Because of our focus on low birth weight as primary determinant, supportive measures to enhance enrolment of low birth weight subjects were undertaken. In particular, we adopted a sampling technique in which low birth weight children had a higher chance of being selected, and in the invitation letter we emphasized the importance of their participation. Overall, these measures resulted in an adequate response among low birth weight subjects, although response remained lower than during earlier phases of the ABCD study.

In most chapters of this thesis, we present and discuss participation analyses, which consistently show that children with a higher socioeconomic status and, for studies in the total ABCD cohort, children of Dutch descent were overrepresented in our analyses. The children participating in our add-on study generally had a healthier anthropometric profile, probably because active, normal weight children were more willing to participate in physical fitness tests and PA-related study measurements. This selective participation could have biased the results if the association of birth weight and infant growth with energy balance-related behaviors and physical fitness differed between the included children and the remainder of the ABCD cohort. However unlikely, this cannot be excluded.

IMPLICATIONS FOR PUBLIC HEALTH

With the increased understanding that obesity risk is influenced by early life experiences also comes the realization that measures to prevent obesity need to focus on identifying and minimizing these adverse influences, in addition to the common approach of focusing on adult lifestyle and personal choice. The results described in this thesis suggest that energy balance-related behaviors, physical fitness and autonomic activity, known risk factors of obesity and cardiovascular disease, have a developmental element that is potentially amenable to preventative intervention and monitoring. This key message was raised in a report of the World Health Organization some years ago but has been little acted upon.[67] The failure to recognize the life course nature of risk factors of disease and to incorporate it into public policy may limit capacity to reduce the escalation in the burden of obesity and cardiovascular disease. It is now timely to develop an adequate model of this risk and identify points in the life course at which it is most sensitive to strategies

to reduce it. The findings of this thesis suggest that health promotion strategies should account for the important role of early life nutrition in obesity development by creating supportive environments for those at increased risk of detrimental energy balance-related behaviors and impaired physical fitness, i.e., the low birth weight, accelerated infant weight gain children.

DIRECTIONS FOR FUTURE RESEARCH

Long-term consequences

The observations that early life growth is related to childhood energy balance-related behavior, physical fitness and ANS activity provide new evidence for an underlying pathway of the Developmental Origins of Health and Disease. However, the significance of these associations with regard to later obesity and cardiovascular disease risk remains unclear. Although evidence indicates that energy balance-related behavior and physical fitness track through childhood to adulthood, the implications of their variations due to early growth and development should be topic of future research. Our findings need to be reproduced and followed over time to learn if the early life induced differences in behavior, physical fitness levels and autonomic function are sustained and are ultimately prognostic for obesity and cardiovascular disease in later life. Subsequent measurements within the ABCD cohort, including follow-up measurements of physical fitness, SB and PA at age 11-12 years, will undoubtedly prove valuable on this point.

Underlying mechanisms

There is a lack of physiological insights into the underlying mechanisms and pathways of the associations of early life exposures with energy balance-related behaviors and physical fitness in childhood. We hypothesized that altered autonomic function could mediate early life induced changes in behavior in **Chapter 8**, but we found no supportive evidence. Leptin is another potential mediating candidate. It has been shown that cord leptin levels are diminished in low birth weight children,[68] increase during the catch-up growth[69] and decrease again in adulthood in the context of an excess of adipose tissue when corrected for body fat mass, gender and fasting insulin, suggesting leptin resistance in these individuals.[70] In the brain, leptin interacts with several hypothalamic neuropeptides and reduces food intake, enhances satiety, increases sympathetic activity and stimulates energy expenditure.[71] Because of these effects, there is a potential role of altered leptin secretion and/or sensitivity in the establishment of energy balance-related behaviors in later life.

As mentioned above, epigenetic markers cannot only serve as a biomarker of early life nutritional influences but may also provide insight into the underlying mechanisms involved. Recent studies into the epigenetic effects of early life nutrition used a combination of array discovery techniques to give a measure of the genomic regions in which epigenetic changes may be manifest, followed by more in depth analysis of candidate regions. These studies demonstrated several nutrition-induced epigenetic mechanisms acting within several major molecular pathways of obesity. For example, diet-induced obese mice showed perturbations in DNA methylation of the leptin promotor and other appetite-regulating peptides (i.e., neuropeptide Y and proopiomelanocortin peptide).[72] There is also evidence of additional early life-induced epigenetic regulation of pathways related to energy expenditure (e.g., ornithine Decarboxylase [ODC] and spermidine-spermine N-acetyltransferase [SSAT]), fat accumulation (e.g., CCAAT/enhancer binding protein alpha [CEBPA],peroxisome proliferator-activated receptor gamma [PPARG] and fatty acid synthase [FASN]) and hedonic eating behaviors (e.g., tyrosine hydroxylase [TH], dopamine transporter solute carrier family 6 [SLC6A3] and cyclin-dependent kinase inhibitor 1C [CDKN1C]).[72, 73] As this field progresses, the relevance of epigenetic changes for later energy balance-related behavior and physical fitness is likely to become more apparent. Such markers could be measured in early life and used to indicate the most effective interventions and to monitor their efficacy.

The role of formula feeding

Compelling evidence indicates that infant formula feeding rather than human breast milk conveys a greater risk of later obesity.[75] The stable calorie-dense composition of formula milk could induce accelerated infant weight gain, and may signal a rich environment when in reality it is more nutritionally constrained. In addition, intake of formula milk may be more directly driven by parental behavior than by infant demand.[75] Both aspects could influence appetite and satiety response, which therefore provides a potential mechanism by which nutritional influences in infancy may affect energy balance-related behavior in childhood.

A further issue which merits consideration is the composition of the formula, especially its protein content.[76] Preliminary evidence suggests that a lower protein composition reduces the accelerated infant weight gain associated with infant feeding. High-quality randomized controlled trials on this matter are currently underway and could add to our current understanding on the role of infant feeding on infant growth, body composition and appetite.[77]

Intervention studies

Several groups have explored the concept that an intervention given during development, either to the mother or her offspring, can reduce or prevent the detrimental effects of dietary mismatch on her offspring. For example, leptin administration to the newborn rat prevents hyperphagia, adiposity, and other detrimental effects of mismatch produced by global undernourishment of the dam followed by feeding the pups a high-fat diet.[78] It also reversed effects of maternal undernutrition on the expression of candidate genes through epigenetic signaling.[79] While these animal experiments only serve as proof of principle, they offer promise that timely interventions during development may have the potential to reduce the effects of developmental environment in priming behavior, fitness and body composition in the offspring. In this respect, the scientific community has been waiting for human intervention studies and the results of the first human trials on the effect of a prepregnancy maternal lifestyle intervention on the growth, health and lifestyle of the child are highly anticipated.[80]

CONCLUSION

There is a myriad of socioeconomic, behavioral and biological factors that have contributed and continue to add to the worldwide epidemic obesity and cardiovascular disease. The Developmental Origins of Health and Disease appears to be another element that warrants serious consideration. The studies presented in this thesis suggest that suboptimal growth in infancy is associated with unfavorable energy balance-related behavior and impaired physical fitness in childhood. Additionally, low birth weight was associated with impaired autonomic activity in children. We are still far from having clarified the implications of these early life influences on later disease risk as well as understanding the mechanisms by which adverse perinatal nutritional stimuli may sensitize to unfavorable energy balance-related behaviors, impaired physical fitness and altered autonomic activity. At the heart of this challenge lies the fundamental question whether these components are potentially amenable to preventative intervention through the optimization of prenatal and postnatal growth and monitoring through the use of markers signaling increased risk of obesity and cardiovascular disease.

An important task for future research is to confirm our conclusions and to examine the effects of energy balance-related behaviors and physical fitness in childhood on later disease risk. The implications of such new perspectives could be far-reaching. They are of direct relevance to the initiatives that address the challenge of obesity globally, by taking into account the potential importance of early life influences in interventions and in targeting those at highest risk for developmentally induced obesity and cardiovascular

disease. In other words, future public health policies aimed at tackling obesity could benefit from incorporating the optimization of energy balance-related behavior and physical fitness, potentially through the optimization of early life growth.

A healthy growth strategy is needed.

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10. ENGLISH SUMMARY

Obesity is considered one of the biggest threats to global health of the 21st century. It is associated with a wide range of serious health complications and with an increased risk of premature onset of illnesses, including diabetes and cardiovascular disease. A large body of evidence now suggests that susceptibility for obesity and cardiovascular disease at least partly originate in early life, with increased risks associated with unbalanced maternal diet, placental insufficiency or postnatal nutritional excesses. This field is known as the Developmental Origins of Health and Disease (DOHaD). It warrants serious consideration from a public health perspective, because this may eventually lead to new public health strategies for obesity prevention and for identification of groups at risk. In search of the underlying mechanisms linking early life with later disease, a hypothesis emerged that linked suboptimal early life nutrition with unfavorable later energy balance-related behaviors, encompassing energy intake, eating behavior, physical activity (PA) and sedentary behavior (SB), and reduced physical fitness levels. This might, in turn, increase later disease risk.

To study the role of prenatal and early postnatal growth, as measured by birth weight and infant growth, respectively, in childhood energy balance-related behaviors and physical fitness, we formulated the following research questions:

1. What is the currently available evidence for the association of birth weight and infant growth with energy balance-related behavior in humans?
2. What is the association of birth weight and infant growth with childhood energy intake and eating behavior?
3. What is the association of birth weight and infant growth with childhood PA and SB?
4. What is the association of birth weight and infant growth with childhood physical fitness?
5. Does autonomic nervous system (ANS) activity mediate a potential association of birth weight and infant growth with energy balance-related behaviors in children?

An introduction to the relevance of early life influences to the current obesity pandemic and the potential underlying role of energy balance-related behaviors and physical fitness is outlined in **Chapter 1**. This chapter provides a narrative overview of the studies that led to the current state of the DOHaD paradigm, as well as the preliminary evidence for physical fitness, energy balance-related behavior and ANS activity to be parts of the pathway from early life nutrition to adult onset disease. In **Chapter 2**, the aims and outline of this thesis are presented, as well as an overview of the Amsterdam Born Children and their Development (ABCD) cohort, in which the studies of this thesis were embedded. The ABCD study is a prospective community-based cohort study initiated in 2003 by the Municipal Health Service, the Academic Medical Center and the VU University Medical

Center. One of the objectives of the ABCD study is to gain more insight into early life conditions and the extent to which these conditions explain children's health in later life. In this cohort, data was collected by questionnaires completed by mothers and their children, child health care registration and hands-on measurements. **Chapter 3** describes the rationale and design of an add-on study. This study was conducted within the framework of the ABCD study and designed and coordinated by the author of this thesis. The study was developed to examine the association of birth weight and infant growth trajectories with physical fitness, PA levels and SB in a subgroup of 194 children of the ABCD study, who were 8-9 years old at the time.

In **Chapter 4**, we present the results of a systematic review on the association of birth size or infant growth with later energy intake, eating behaviors, PA or SB in humans. We appraised the methodological quality of the studies and synthesized the extracted data through a best-evidence synthesis. Based on 41 relevant publications of overall low methodological quality, we found no evidence for an association of birth weight with later energy intake, eating behavior, PA or SB. There was moderate evidence for an association of extreme birth weights (at both ends of the spectrum) with lower PA levels at a later age. Evidence for the association of infant growth with energy balance-related behavior was generally insufficient. We concluded that there is a need of high-quality studies on this topic and of studies that appreciate infant growth as a possible determinant of later energy balance-related behaviors.

Chapter 5 focused on energy intake and eating behavior. Here, we present the independent associations of birth weight and postnatal weight and height gain with energy intake and satiety response at 5 years of age. We found that excessive infant and childhood weight gain are associated with increased energy intake and diminished satiety response. Rapid height gain seemed to be beneficial for childhood energy intake. Birth weight was neither related to energy intake nor to satiety response. We argued that the association of postnatal growth with energy intake and satiety response provides a potential mechanism linking early life influences with later obesity and cardiovascular disease.

The independent associations of birth weight and infant growth (in weight, height and body mass index (BMI)) with childhood moderate-to-vigorous PA (MVPA) and SB are described in **Chapter 6**. This study was part of the add-on study addressed in **Chapter 3**. We found that birth weight was not significantly related to MVPA or SB in these children aged 8-9 years. However, children with accelerated infant weight and/or BMI gain were more sedentary in childhood, while children with increased infant height gain engaged in

more MVPA at 8-9 years. These associations were predominantly explained by growth in the first year of life, not the second year.

In **Chapter 7**, we described the association of early growth with physical fitness in childhood in the group of children of the add-on study, and whether these associations are mediated by fat-free mass, MVPA or SB. Intriguingly, we found that children with low birth weight and subsequent accelerated infant weight gain had lower aerobic fitness at 8-9 years of age. This in contrast to children with only low birth weight (with normal infant weight gain) or only accelerated infant weight gain (after normal birth weight), who had a similar aerobic fitness level to children with normal birth weight and normal infant weight gain. This finding supports the 'mismatch concept', indicating that the combination of prenatal undernutrition with postnatal overnutrition is particularly detrimental for later health. In addition, we found a positive association of birth weight with neuromuscular fitness. This was for more than 75% mediated by differences in fat-free mass. Infant growth expressed as BMI gain (instead of weight gain), however, was associated with reduced neuromuscular fitness. This was not mediated by either fat-free mass, MVPA or SB.

In **Chapter 8**, we turned our attention to the ANS, and how autonomic function relates to early growth. Because autonomic activity has repeatedly been associated with altered behavior in childhood, including impulsivity and sensitivity to food reward, we additionally assessed whether variations in autonomic activity could explain the effects of early growth on energy-balance related behaviors. We found that children with low birth weight had increased sympathetic nervous system activity compared to normal birth weight children, which is considered unfavorable for later health. Infant height gain was associated with a more favorable, decreased sympathetic activity. Levels of sympathetic activity, however, did not mediate the associations of suboptimal perinatal growth with detrimental energy balance-related behaviors. There was no shift in parasympathetic activity associated with either birth weight or infant growth.

Chapter 9 is dedicated to a reflection on the main findings of this thesis. We discuss the broader perspective and potential clinical relevance of our results and consider the clinical and methodological limitations of our studies. We also reflect on the implications of our findings for public health policies, and propose directions for future research on the Developmental Origins of Energy Balance-Related Behavior and Physical Fitness. In short, main conclusions drawn from the findings of this thesis are:

- There is no evidence to support the hypothesis that birth weight (as a proxy for prenatal nutrition) is associated with any of the studied energy balance-related behaviors, i.e., energy intake, eating behavior, PA or SB, in the human population;

- Postnatal growth, more than prenatal growth, is associated with energy balance-related behaviors and physical fitness levels in childhood;
- The definition of postnatal growth is of crucial importance when studying the Developmental Origins of Energy Balance-Related Behaviors and Physical Fitness levels, because the associations with the different outcomes vary greatly between weight gain, BMI gain, and linear growth, and between the different periods of growth. In general, we observed detrimental associations with weight and BMI gain and beneficial associations with height gain, especially when growth was confined to the period of early infancy (i.e., the first year of life);
- Perinatal growth is associated with childhood ANS function, but the implications on later disease risk should probably be sought outside behavioral processes, as ANS activity did not mediate any of the associations of birth weight or infant growth with energy balance-related behaviors.

11. NEDERLANDSE SAMENVATTING

Obesitas is één van de grootste volksgezondheidsproblemen van de 21ste eeuw. Het heeft negatieve effecten op gezondheid en welbevinden en vergroot het risico op andere welvaartziektes, zoals diabetes mellitus en hart- en vaatziekten. Er is steeds meer wetenschappelijk bewijs voorhanden dat de aanleg voor obesitas en hart- en vaatziekten gedeeltelijk gevormd wordt door omgevingsinvloeden uit het vroege leven. Zo is het latere risico op obesitas en hart- en vaatziekten verhoogd na een ongezond maternaal dieet tijdens de zwangerschap, placentaire dysfunctie of overvoeding direct postnataal. Het wetenschappelijk vakgebied dat dit onderzoekt staat bekend als de "Developmental Origins of Health and Disease" (DOHaD). Investering in deze relatief nieuwe wetenschap kan leiden tot nieuwe strategieën in de strijd tegen obesitas en hart- en vaatziekten, en kan de groepen identificeren die een hoog risico lopen op latere ziekten door vroege omgevingsinvloeden.

De onderliggende mechanismen, waarmee vroege omgevingsinvloeden het latere ziekterisico beïnvloeden, is onderwerp van veel onderzoek vandaag de dag. Eén hypothese stelt dat voeding, en daarmee groei, vóór en vlak na de geboorte het gedrag en de fysieke fitheid van een persoon in het latere leven beïnvloedt. Ongunstig gedrag samenhangend met de energiebalans, zoals verminderde fysieke activiteit, toegenomen sedentair gedrag en slechte eetgewoontes, en een matige fysieke fitheid kan vervolgens weer het gezondheidsrisico beïnvloeden.

Om de effecten van prenatale en vroege postnatale groei, gemeten als respectievelijk geboortegewicht en groei op de zuigelingenleeftijd, op het met de energiebalans samenhangend gedrag en fysieke fitheid te bestuderen, hebben we de volgende onderzoeksvragen geformuleerd:

1. Wat is het huidige wetenschappelijk bewijs voor een associatie van geboortegewicht en groei op de zuigelingenleeftijd met gedrag samenhangend met de energiebalans bij mensen?
2. Wat is de associatie van geboortegewicht en groei op de zuigelingenleeftijd met energie-inname en eetgedrag bij kinderen?
3. Wat is de associatie van geboortegewicht en groei op de zuigelingenleeftijd met fysieke activiteit en sedentair gedrag bij kinderen?
4. Wat is de associatie van geboortegewicht en groei op de zuigelingenleeftijd met fysieke fitheid bij kinderen?
5. Verklaart een verandering in de activiteit van het autonome zenuwstelsel de associaties van geboortegewicht en groei op de zuigelingenleeftijd met gedrag samenhangend met de energiebalans?

Het belang van omgevingsinvloeden uit het vroege leven op de huidige obesitasepidemie, en een mogelijke onderliggende rol van het met de energiebalans samenhangend gedrag en fysieke fitheid, wordt toegelicht in **Hoofdstuk 1**. Dit hoofdstuk geeft een overzicht van de studies die hebben geleid tot de huidige DOHaD wetenschap, alsook een overzicht van het eerste bewijs dat met de energiebalans samenhangend gedrag, fysieke fitheid en het autonome zenuwstelsel onderdeel uitmaakt van het onderliggend verband tussen voeding rondom de geboorte en het latere ziekterisico. In **Hoofdstuk 2** omschrijven wij de onderzoeksvragen en de opzet van dit proefschrift, en geven we een overzicht van het Amsterdam Born Children and their Development (ABCD) cohort. In dit cohort zijn de studies van dit proefschrift verricht. De ABCD studie is een prospectief, populatiebreed cohortonderzoek, dat in 2003 is opgericht door de Gemeentelijke Gezondheidsdienst, het Academisch Medisch Centrum en het VU medisch centrum. Eén van de doelen van de ABCD studie is om meer inzicht te krijgen in de invloed van vroege omgevingsinvloeden en hoe dit de latere gezondheid bepaald. De ABCD studie maakt gebruik van vragenlijsten ingevuld door de moeders en hun kinderen, GGD registraties, en directe metingen. In **Hoofdstuk 3** presenteren wij de opzet en onderbouwing van een extra onderzoeksonderdeel binnen de ABCD studie, ontwikkeld en gecoördineerd door de auteur van dit proefschrift. Dit extra onderzoek was opgericht om specifiek de associatie van geboortegewicht en groei op de zuigelingenleeftijd met fysieke fitheid, fysieke activiteit en sedentair gedrag te onderzoeken in een subgroep van 194 kinderen van de ABCD studie. Deze kinderen waren 8-9 jaar oud tijdens de metingen.

In **Hoofdstuk 4** hebben wij systematisch de wetenschappelijke literatuur doorzocht naar studies over de associatie van geboorteafmetingen en zuigelingengroei met latere energie-inname, eetgedrag, fysieke activiteit en sedentair gedrag bij mensen. We hebben de methodologische kwaliteit beoordeeld en de gegevens uit deze studies samengevoegd via een 'best-evidence' synthese. We identificeerden 41 relevante publicaties, vooral van slechte methodologische kwaliteit. Hierin vonden we geen bewijs voor een associatie van geboortegewicht met latere energie-inname, eetgedrag, fysieke activiteit of sedentair gedrag bij mensen. Er was matig-sterk bewijs dat een extreem hoog of laag geboortegewicht geassocieerd was met minder fysieke activiteit op latere leeftijd. Er was onvoldoende bewijs voor de associatie van zuigelingengroei met de uitkomstmaten. Onze conclusie was dat er meer studies van hoge methodologische kwaliteit nodig zijn op dit onderzoeksvlak, in het bijzonder onderzoek naar de invloed van zuigelingengroei op het met de energiebalans samenhangend gedrag.

Hoofdstuk 5 richtte zich op energie-inname en eetgedrag. Hierin presenteren we de onafhankelijke associaties van geboortegewicht en gewichts- en lengtetoename op de zuigelingenleeftijd met energie-inname en verzadigingsgevoel op vijfjarige leeftijd. We

vonden dat overmatige gewichtstoename op zuigelingen- of kinderleeftijd geassocieerd was met meer energie-inname en minder verzadigingsgevoel op vijfjarige leeftijd. Snelle lengtegroei lijkt juist gunstig voor latere energie-inname. Geboortegewicht was niet geassocieerd met energie-inname of verzadigingsgevoel op vijfjarige leeftijd. Dit zou een eerste bewijs kunnen zijn voor een onderliggende rol van energie-inname en verzadigingsgevoel in de associatie van suboptimale groei in de vroege kinderleeftijd met een groter risico op obesitas en hart- en vaatziekten.

De onafhankelijke associaties van geboortegewicht en gewichts-, lengte- en BMI-toename op de zuigelingenleeftijd met (matig-)intensieve fysieke activiteit en sedentair gedrag zijn beschreven in **Hoofdstuk 6**. Dit komt voort uit het extra onderzoeksonderdeel beschreven in **Hoofdstuk 3**. We vonden geen associatie van geboortegewicht met fysieke activiteit of sedentair gedrag bij deze 8- en 9-jaar oude kinderen. Kinderen met overmatige gewichts- of BMI-toename als zuigeling vertoonden echter meer sedentair gedrag op 8/9-jarige leeftijd, terwijl kinderen met snelle lengtegroei meer fysieke activiteit vertoonden. Opvallend was dat vooral groei in het eerste levensjaar van belang lijkt in dit verband, niet groei in het tweede levensjaar.

In **Hoofdstuk 7** beschrijven we de associatie van vroege groei met fysieke fitheid bij de kinderen uit het extra onderzoeksonderdeel. Tevens onderzochten we of deze verbanden konden worden verklaard door de hoeveelheid vetvrije massa van de kinderen, of door de hoeveelheid fysieke activiteit of sedentair gedrag. We vonden dat kinderen met een laag geboortegewicht gevolgd door een snelle gewichtstoename op zuigelingenleeftijd een verminderd uithoudingsvermogen hadden op 8/9-jarige leeftijd. Verrassend genoeg was dit niet het geval voor kinderen met alleen een laag geboortegewicht (gevolgd door normale gewichtstoename) of alleen snelle gewichtstoename op zuigelingenleeftijd (na een normaal geboortegewicht); deze kinderen hadden een uithoudingsvermogen vergelijkbaar met kinderen met een normaal geboortegewicht en normale gewichtstoename. Deze uitkomst ondersteunt het 'mismatch concept' van de DOHaD hypothese, die stelt dat vooral de combinatie van prenatale ondervoeding met postnatale overvoeding nadelige gezondheidseffecten heeft. Tevens vonden we een positief verband van geboortegewicht met latere spierkracht. Dit verband werd voor meer dan 75% verklaard door verschillen in vetvrije massa. Groei op de zuigelingenleeftijd uitgedrukt in BMI toename (in plaats van gewichtstoename) was juist geassocieerd met verminderde spierkracht. Dit verband werd niet verklaard door verschillen in vetvrije massa, fysieke activiteit of sedentair gedrag.

In **Hoofdstuk 8** focusten we ons op het autonome zenuwstelsel, en hoe activiteit van het autonome zenuwstelsel zich verhoudt tot vroege groei. Aangezien deze autonome

activiteit wordt gerelateerd aan gedrag op kinderleeftijd, waaronder impulsiviteit en gevoeligheid voor de belonende waarde van voedsel, hebben we tevens onderzocht of verschillen in autonome activiteit het verband van vroege groei met het met energiebalans samenhangend gedrag bij de kinderen kan verklaren. We vonden dat kinderen met een laag geboortegewicht een verhoogde activiteit hadden van het sympathische zenuwstelsel, vergeleken met kinderen met een normaal geboortegewicht. Dit wordt als ongunstig beschouwd voor latere gezondheid. Lengtegroei op zuigelingenleeftijd was geassocieerd met een gunstigere, verminderde sympathische activiteit. Verschillen in sympathische activiteit verklaarde echter niet het verband van suboptimale groei rondom de geboorte met voor de energiebalans ongunstig gedrag. Er waren geen verschillen in parasympatische activiteit gerelateerd aan geboortegewicht of zuigelingengroei.

In **Hoofdstuk 9** blikken wij terug op de belangrijkste bevindingen van het proefschrift. We plaatsen onze resultaten in een bredere context, verwoorden de potentiële klinische relevantie van de bevindingen, en reflecteren op de klinische en methodologische beperkingen van het onderzoek. Tevens bespreken we wat de consequenties van onze resultaten zijn voor volksgezondheidsbeleid en benoemen we de mogelijkheden voor toekomstig onderzoek naar de ontwikkelingsoorsprong van het met energiebalans samenhangend gedrag en de fysieke fitheid. Samenvattend kunnen op basis van de resultaten van dit proefschrift de volgende conclusies worden getrokken:

- Er is geen bewijs voor de hypothese dat bij mensen geboortegewicht (als maat voor prenatale groei) geassocieerd is met de bestudeerde gedragingen samenhangend met de energiebalans, namelijk energie-inname, eetgedrag, fysieke activiteit en sedentair gedrag;
- Postnatale groei, meer dan prenatale groei, is geassocieerd met gedrag samenhangend met de energiebalans en fysieke fitheid bij kinderen;
- De definitie van groei na de geboorte is essentieel in het onderzoek naar de 'Ontwikkelingsoorsprong van het met energiebalans samenhangend gedrag en de fysieke fitheid', aangezien er grote verschillen zijn in de associaties met de uitkomstmaten tussen groei gedefinieerd als gewichtstoename, BMI-toename en lengtetoename, en tussen de verschillende periodes van groei. In het algemeen vonden we ongunstige associaties met gewichts- en BMI-toename, en gunstige associaties met lengtetoename, vooral wanneer we ons richtten op groei in het eerste levensjaar;
- Vroege groei is gerelateerd aan activiteit van het autonome zenuwstelsel, maar het pad naar een verhoogd later ziekterisico gaat waarschijnlijk niet via veranderd gedrag, aangezien autonome activiteit niet de verklaring was voor de gevonden verbanden van geboortegewicht en zuigelingengroei met gedrag samenhangend met de energiebalans.

SUPPLEMENTARY FILES

SUPPLEMENTARY FILE 3.1.

Amsterdam Born Children and their Development

Physical Activity Questionnaire

We are trying to find out about your level of physical activity from ***the previous 7 days*** (in the previous week). This includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

Remember: **1. There are no right and wrong answers — this is not a test.**
2. Please answer all the questions as honestly and accurately as you can — this is very important.

Should you make a mistake when filling out the questionnaire? Color the box all black and encircle it. Like this: (■). Then tick the appropriate box.

Good luck completing the questionnaire!

Physical activity in your spare time:

1. Have you done any of the following activities in the past 7 days (last week)? If yes, how many times and how long?

Have you done any of the following sports in the past 7 days (last week)?			**If yes: How many times have you done the sport in the past 7 days (last week), and how long each time?**	
Tick NO or YES			**How many times?**	**How long each time?**
Soccer at a sports club	NO ☐	YES ☐		
Soccer on the streets or in a playground	NO ☐	YES ☐		
Tennis at a sports club	NO ☐	YES ☐		
Tennis on the streets or in a playground	NO ☐	YES ☐		
Hockey at a sports club	NO ☐	YES ☐		
Hockey on the streets or in a playground	NO ☐	YES ☐		
Basketball at a sports club	NO ☐	YES ☐		
Basketball on the streets or in a playground	NO ☐	YES ☐		
Gymnastic sports	NO ☐	YES ☐		
Baseball or softball at a sports club	NO ☐	YES ☐		
Baseball or softball on the streets or in a playground	NO ☐	YES ☐		
Table tennis at a sports club	NO ☐	YES ☐		
Table tennis on the streets or in a playground	NO ☐	YES ☐		
Badminton at a sports club	NO ☐	YES ☐		

Badminton on the streets or in a playground	NO ☐	YES ☐		
Volleyball at a sports club	NO ☐	YES ☐		
Volleyball on the streets or in a playground	NO ☐	YES ☐		
Netball at a sports club	NO ☐	YES ☐		
Netball on the streets or in a playground	NO ☐	YES ☐		
Handball at a sports club	NO ☐	YES ☐		
Handball on the streets or in a playground	NO ☐	YES ☐		
Martial arts (such as judo, karate, kickboxing)	NO ☐	YES ☐		
Dance (such as ballet, street dance, jazz ballet)	NO ☐	YES ☐		
Ice skating	NO ☐	YES ☐		
Athletics	NO ☐	YES ☐		
Swimming laps	NO ☐	YES ☐		
Swimming for fun	NO ☐	YES ☐		
Cycling	NO ☐	YES ☐		
Other sports? Please state ……				
Have you done any of the following activities in the past 7 days (last week)?			**If yes: How many times have you done the sport in the past 7 days (last week), and how long each time?**	
Tick NO or YES			**How many times?**	**How long each time?**
Playing tag	NO ☐	YES ☐		
Skipping rope	NO ☐	YES ☐		

Bounce on the trampoline	NO ☐	YES ☐		
Play on playground equipment	NO ☐	YES ☐		
Play in the cubby house	NO ☐	YES ☐		
Jogging or running	NO ☐	YES ☐		
Roller blading	NO ☐	YES ☐		
Skateboarding	NO ☐	YES ☐		
Scooter	NO ☐	YES ☐		
Play with pets	NO ☐	YES ☐		
Walk the dog	NO ☐	YES ☐		
Bike riding in your free time	NO ☐	YES ☐		
Physical education class	NO ☐	YES ☐		
Sport class at school	NO ☐	YES ☐		
Travel by walking to school (to and from school = 2 times)	NO ☐	YES ☐		
Travel by cycling to school (to and from school = 2 times)	NO ☐	YES ☐		
Watching TV / videos / DVD	NO ☐	YES ☐		
Playing Playstation / Nintendo / Wii / DS / XBOX / computer games	NO ☐	YES ☐		
Other computer / Internet use	NO ☐	YES ☐		
Homework	NO ☐	YES ☐		
Playing indoors with toys	NO ☐	YES ☐		

Sitting talking	NO ☐	YES ☐		
Talk on the phone	NO ☐	YES ☐		
Listen to music	NO ☐	YES ☐		
Playing a musical instrument	NO ☐	YES ☐		
Playing board games / card games	NO ☐	YES ☐		
Reading	NO ☐	YES ☐		
Art & craft (such as pottery, sewing, drawing)	NO ☐	YES ☐		
Household chores (such as dishwashing, vacuuming, washing the car)	NO ☐	YES ☐		
Imaginary play	NO ☐	YES ☐		
Travel by car/bus to school (to and from school = 2 times)	NO ☐	YES ☐		

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

- ☐ I don't do PE
- ☐ Hardly ever
- ☐ Sometimes
- ☐ Quite often
- ☐ Always

3. In the last 7 days, what did you do most of the time at recess? (Check one only.)

- ☐ Sat down (talking, reading, doing schoolwork)
- ☐ Stood around or walked around
- ☐ Ran or played a little bit
- ☐ Ran around and played quite a bit
- ☐ Ran and played hard most of the time

4. In the last 7 days, what did you normally do at lunch (besides eating lunch)? (Check one only.)

- ☐ Sat down (talking, reading, doing schoolwork)
- ☐ Stood around or walked around
- ☐ Ran or played a little bit
- ☐ Ran around and played quite a bit
- ☐ Ran and played hard most of the time

5. In the last 7 days, on how many days right after school, did you do sports, dance, or play games in which you were very active? (Check one only.)

- ☐ None
- ☐ 1 time last week
- ☐ 2 or 3 times last week
- ☐ 4 times last week
- ☐ 5 times last week

6. In the last 7 days, on how many evenings did you do sports, dance, or play games in which you were very active? (Check one only.)

☐ None
☐ 1 time last week
☐ 2 or 3 times last week
☐ 4 or 5 times last week
☐ 6 or 7 times last week

7. On the last weekend, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

☐ None
☐ 1 time last week
☐ 2 or 3 times last week
☐ 4 or 5 times last week
☐ 6 or more times last week

8. Which one of the following describes you best for the last 7 days? Read all five statements, and encircle the one answer that describes you best.

A. All or most of my free time was spent doing things that involve little physical effort.
B. I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics).
C. I often (3 — 4 times last week) did physical things in my free time.
D. I quite often (5 — 6 times last week) did physical things in my free time.
E. I very often (7 or more times last week) did physical things in my free time.

9. Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

Monday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Tuesday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Wednesday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Thursday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Friday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Saturday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐
Sunday	None ☐	Little bit ☐	Medium ☐	Often ☐	Very often ☐

10. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

☐ NO
☐ YES

If YES, what prevented you? _____

End of the questionnaire. Thank you for completing!

SUPPLEMANTARY FILE 4.1. FULL LITERATURE SEARCH AND NUMBER OF REFERENCES.

Search date	15-1-2013	Update 3-7-2014	Update 19-5-2015	Update 5-1-2016
Pubmed	2898	3275	3514	3724
Embase	2356	3773	2879	3061
PsycInfo	490	527	548	577
Cochrane	705	402	482	545
Total	**6369**	**7977**	**7423**	**7907**
After deduplication	**5530**	**6853**	**6231**	**6688**

Methods: Liberati *et al.*, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate helath care interventions: explanation and elaboration. 2009, Journal of Clinical Epidemiology; 62: e1-e34.

1. Pubmed

#1 Perinatal influences
Birth weight[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR dohad[tiab] OR (("Birth weight"[tiab] OR "Perinatal"[tiab] OR "infant growth"[tiab] OR "fetal"[tiab] OR "intra-uterine growth"[tiab] OR "infant programming"[tiab] OR "intra-uterine programming"[tiab] OR "developmental programming"[tiab] OR "intra-uterine plasticity"[tiab] OR "developmental plasticity"[tiab] OR developmental origin*[tiab] OR early-life origin*[tiab] OR intra-uterine origin*[tiab] OR developmental influence*[tiab] OR early-life influence*[tiab] OR intra-uterine influence*[tiab] OR famine[tiab] OR "catch-up growth"[tiab] OR "accelerated growth"[tiab] OR "Small for Gestational Age"[tiab] OR dysmaturity[tiab]) NOT medline[sb])

#2 Energy-balance related behavior
Physical activity - Sedentary behavior - Eating behavior – Energy intake

"Exercise"[Majr:NoExp] OR "Running"[Mesh] OR "Swimming"[Mesh:noexp] OR "Walking"[Mesh:noexp] OR "Sports"[Mesh] OR "Life Style"[Mesh:NoExp] OR "Sedentary Lifestyle"[Mesh] OR "Appetite"[Mesh] OR "Health Behavior"[Majr:NoExp] OR "Feeding Behavior"[Mesh] OR "physical activity"[tiab] OR appetit*[tiab] OR satiety[tiab] OR "childhood diet"[tiab] OR ((sport*[tiab] OR exercise*[tiab] OR "activity level"[tiab] OR "motor activity"[tiab] OR "locomotor activity"[tiab] OR "sedentary"[tiab] OR sedentarism[tiab] OR sedentariness[tiab] OR "physical inactivity"[tiab] OR "sitting"[tiab] OR "diet behavior"[tiab] OR "dietary behavior"[tiab] OR "feeding behavior"[tiab] OR "appetitive behavior"[tiab]

OR "diet behaviour"[tiab] OR "dietary behaviour"[tiab] OR "feeding behaviour"[tiab] OR "appetitive behaviour"[tiab] OR diet preference*[tiab] OR dietary preference*[tiab] OR feeding preference*[tiab] OR diet habit*[tiab] OR dietary habit*[tiab] OR feeding habit*[tiab] OR "feeding practice"[tiab] OR "feeding practices"[tiab] OR "diet regulation"[tiab] OR "feeding regulation"[tiab] OR "diet control"[tiab] OR "dietary control"[tiab] OR "feeding control"[tiab] OR hunger[tiab] OR hyperphagia[tiab] OR hyperphagic[tiab] OR "energy expenditure"[tiab] OR "energy level"[tiab]) NOT medline[sb])

#3 Publication types filter:

NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type])

Search	PubMed Query 15-01-2013	Items found
#6	Search **#4 AND #5**	12
#5	Search **20493499[uid] OR 15997047[uid] OR 23049962[uid] OR 23251693[uid] OR 21167701[uid] OR 16234423[uid] OR 19064527[uid] OR 16404403[uid] OR 16339179[uid] OR 15469656[uid] OR 22595039[uid] OR 18761782[uid]**	12
#4	Search **#3 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type])**	2898
#3	Search **#1 AND #2**	3004
#2	Search **"Exercise"[Majr:NoExp] OR "Running"[Mesh] OR "Swimming"[Mesh:noexp] OR "Walking"[Mesh:noexp] OR "Sports"[Mesh] OR "Life Style"[Mesh:NoExp] OR "Sedentary Lifestyle"[Mesh] OR "Appetite"[Mesh] OR "Health Behavior"[Majr:NoExp] OR "Feeding Behavior"[Mesh] OR "physical activity"[tiab] OR appetit*[tiab] OR satiety[tiab] OR "childhood diet"[tiab] OR ((sport*[tiab] OR exercise*[tiab] OR "activity level"[tiab] OR "motor activity"[tiab] OR "locomotor activity"[tiab] OR "sedentary"[tiab] OR sedentarism[tiab] OR sedentariness[tiab] OR "physical inactivity"[tiab] OR "sitting"[tiab] OR "diet behavior"[tiab] OR "dietary behavior"[tiab] OR "feeding behavior"[tiab] OR "appetitive behavior"[tiab] OR "diet behaviour"[tiab] OR "dietary behaviour"[tiab] OR "feeding behaviour"[tiab] OR "appetitive behaviour"[tiab] OR diet preference*[tiab] OR dietary preference*[tiab] OR feeding preference*[tiab] OR diet habit*[tiab] OR dietary habit*[tiab] OR feeding habit*[tiab] OR "feeding practice"[tiab] OR "feeding practices"[tiab] OR "diet regulation"[tiab] OR "feeding regulation"[tiab] OR "diet control"[tiab] OR "dietary control"[tiab] OR "feeding control"[tiab] OR hunger[tiab] OR hyperphagia[tiab] OR hyperphagic[tiab] OR "energy expenditure"[tiab] OR "energy level"[tiab]) NOT medline[sb])**	355277
#1	Search **Birth weight[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR dohad[tiab] OR (("Birth weight"[tiab] OR "Perinatal"[tiab] OR "infant growth"[tiab] OR "fetal"[tiab] OR "intra-uterine growth"[tiab] OR "infant programming"[tiab] OR "intra-uterine programming"[tiab] OR "developmental programming"[tiab] OR "intra-uterine plasticity"[tiab] OR "developmental plasticity"[tiab] OR developmental origin*[tiab] OR early-life origin*[tiab] OR intra-uterine origin*[tiab] OR developmental influence*[tiab] OR early-life influence*[tiab] OR intra-uterine influence*[tiab] OR famine[tiab] OR "catch-up growth"[tiab] OR "accelerated growth"[tiab] OR "Small for Gestational Age"[tiab] OR dysmaturity[tiab]) NOT medline[sb])**	80276

Search	PunMed Query 03-07-2014	Items found
#4	Search **#3 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type])**	3275
#3	Search **#1 AND #2**	3392
#2	Search **"Exercise"[Majr:NoExp] OR "Running"[Mesh] OR "Swimming"[Mesh:noexp] OR "Walking"[Mesh:noexp] OR "Sports"[Mesh] OR "Life Style"[Mesh:NoExp] OR "Sedentary Lifestyle"[Mesh] OR "Appetite"[Mesh] OR "Health Behavior"[Majr:NoExp] OR "Feeding Behavior"[Mesh] OR "physical activity"[tiab] OR appetit*[tiab] OR satiety[tiab] OR "childhood diet"[tiab] OR ((sport*[tiab] OR exercise*[tiab] OR "activity level"[tiab] OR "motor activity"[tiab] OR "locomotor activity"[tiab] OR "sedentary"[tiab] OR sedentarism[tiab] OR sedentariness[tiab] OR "physical inactivity"[tiab] OR "sitting"[tiab] OR "diet behavior"[tiab] OR "dietary behavior"[tiab] OR "feeding behavior"[tiab] OR "appetitive behavior"[tiab] OR "diet behaviour"[tiab] OR "dietary behaviour"[tiab] OR "feeding behaviour"[tiab] OR "appetitive behaviour"[tiab] OR diet preference*[tiab] OR dietary preference*[tiab] OR feeding preference*[tiab] OR diet habit*[tiab] OR dietary habit*[tiab] OR feeding habit*[tiab] OR "feeding practice"[tiab] OR "feeding practices"[tiab] OR "diet regulation"[tiab] OR "feeding regulation"[tiab] OR "diet control"[tiab] OR "dietary control"[tiab] OR "feeding control"[tiab] OR hunger[tiab] OR hyperphagia[tiab] OR hyperphagic[tiab] OR "energy expenditure"[tiab] OR "energy level"[tiab]) NOT medline[sb])**	408780
#1	Search **Birth weight[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR dohad[tiab] OR (("Birth weight"[tiab] OR "Perinatal"[tiab] OR "infant growth"[tiab] OR "fetal"[tiab] OR "intra-uterine growth"[tiab] OR "infant programming"[tiab] OR "intra-uterine programming"[tiab] OR "developmental programming"[tiab] OR "intra-uterine plasticity"[tiab] OR "developmental plasticity"[tiab] OR developmental origin*[tiab] OR early-life origin*[tiab] OR intra-uterine origin*[tiab] OR developmental influence*[tiab] OR early-life influence*[tiab] OR intra-uterine influence*[tiab] OR famine[tiab] OR "catch-up growth"[tiab] OR "accelerated growth"[tiab] OR "Small for Gestational Age"[tiab] OR dysmaturity[tiab]) NOT medline[sb])**	89121

Search	PubMed Query 19-05-2015	Items found
#4	Search **#3 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type])**	3514
#3	Search **#1 AND #2**	3640
#2	Search **"Exercise"[Majr:NoExp] OR "Running"[Mesh] OR "Swimming"[Mesh:noexp] OR "Walking"[Mesh:noexp] OR "Sports"[Mesh] OR "Life Style"[Mesh:NoExp] OR "Sedentary Lifestyle"[Mesh] OR "Appetite"[Mesh] OR "Health Behavior"[Majr:NoExp] OR "Feeding Behavior"[Mesh] OR "physical activity"[tiab] OR appetit*[tiab] OR satiety[tiab] OR "childhood diet"[tiab] OR ((sport*[tiab] OR exercise*[tiab] OR "activity level"[tiab] OR "motor activity"[tiab] OR "locomotor activity"[tiab] OR "sedentary"[tiab] OR sedentarism[tiab] OR sedentariness[tiab] OR "physical inactivity"[tiab] OR "sitting"[tiab] OR "diet behavior"[tiab] OR "dietary behavior"[tiab] OR "feeding behavior"[tiab] OR "appetitive behavior"[tiab] OR "diet behaviour"[tiab] OR "dietary behaviour"[tiab] OR "feeding behaviour"[tiab] OR "appetitive behaviour"[tiab] OR diet preference*[tiab] OR dietary preference*[tiab] OR feeding preference*[tiab] OR diet habit*[tiab] OR dietary habit*[tiab] OR feeding habit*[tiab] OR "feeding practice"[tiab] OR "feeding practices"[tiab] OR "diet regulation"[tiab] OR "feeding regulation"[tiab] OR "diet control"[tiab] OR "dietary control"[tiab] OR "feeding control"[tiab] OR hunger[tiab] OR hyperphagia[tiab] OR hyperphagic[tiab] OR "energy expenditure"[tiab] OR "energy level"[tiab]) NOT medline[sb])**	436156
#1	Search **Birth weight[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR dohad[tiab] OR (("Birth weight"[tiab] OR "Perinatal"[tiab] OR "infant growth"[tiab] OR "fetal"[tiab] OR "intra-uterine growth"[tiab] OR "infant programming"[tiab] OR "intra-uterine programming"[tiab] OR "developmental programming"[tiab] OR "intra-uterine plasticity"[tiab] OR "developmental plasticity"[tiab] OR developmental origin*[tiab] OR early-life origin*[tiab] OR intra-uterine origin*[tiab] OR developmental influence*[tiab] OR early-life influence*[tiab] OR intra-uterine influence*[tiab] OR famine[tiab] OR "catch-up growth"[tiab] OR "accelerated growth"[tiab] OR "Small for Gestational Age"[tiab] OR dysmaturity[tiab]) NOT medline[sb])**	94299

Search	PubMed Query 05-01-2016	Items found
#52	Search **#51 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type])**	3724
#51	Search **#49 AND #50**	3855
#50	Search **"Exercise"[Majr:NoExp] OR "Running"[Mesh] OR "Swimming"[Mesh:noexp] OR "Walking"[Mesh:noexp] OR "Sports"[Mesh] OR "Life Style"[Mesh:NoExp] OR "Sedentary Lifestyle"[Mesh] OR "Appetite"[Mesh] OR "Health Behavior"[Majr:NoExp] OR "Feeding Behavior"[Mesh] OR "physical activity"[tiab] OR appetit*[tiab] OR satiety[tiab] OR "childhood diet"[tiab] OR ((sport*[tiab] OR exercise*[tiab] OR "activity level"[tiab] OR "motor activity"[tiab] OR "locomotor activity"[tiab] OR "sedentary"[tiab] OR sedentarism[tiab] OR sedentariness[tiab] OR "physical inactivity"[tiab] OR "sitting"[tiab] OR "diet behavior"[tiab] OR "dietary behavior"[tiab] OR "feeding behavior"[tiab] OR "appetitive behavior"[tiab] OR "diet behaviour"[tiab] OR "dietary behaviour"[tiab] OR "feeding behaviour"[tiab] OR "appetitive behaviour"[tiab] OR diet preference*[tiab] OR dietary preference*[tiab] OR feeding preference*[tiab] OR diet habit*[tiab] OR dietary habit*[tiab] OR feeding habit*[tiab] OR "feeding practice"[tiab] OR "feeding practices"[tiab] OR "diet regulation"[tiab] OR "feeding regulation"[tiab] OR "diet control"[tiab] OR "dietary control"[tiab] OR "feeding control"[tiab] OR hunger[tiab] OR hyperphagia[tiab] OR hyperphagic[tiab] OR "energy expenditure"[tiab] OR "energy level"[tiab]) NOT medline[sb])**	467128
#49	Search **Birth weight[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR dohad[tiab] OR (("Birth weight"[tiab] OR "Perinatal"[tiab] OR "infant growth"[tiab] OR "fetal"[tiab] OR "intra-uterine growth"[tiab] OR "infant programming"[tiab] OR "intra-uterine programming"[tiab] OR "developmental programming"[tiab] OR "intra-uterine plasticity"[tiab] OR "developmental plasticity"[tiab] OR developmental origin*[tiab] OR early-life origin*[tiab] OR intra-uterine origin*[tiab] OR developmental influence*[tiab] OR early-life influence*[tiab] OR intra-uterine influence*[tiab] OR famine[tiab] OR "catch-up growth"[tiab] OR "accelerated growth"[tiab] OR "Small for Gestational Age"[tiab] OR dysmaturity[tiab]) NOT medline[sb])**	98722

2. EMBASE.com

#1 Perinatal influences/ DOHaD

'birth weight'/exp OR 'prenatal exposure'/exp OR dohad:ti,ab OR 'Perinatal growth':ti,ab OR 'infant growth':ti,ab OR 'intra-uterine growth':ti,ab OR 'intra-uterine programming':ti,ab OR 'developmental programming':ti,ab OR 'developmental origin':ti,ab OR 'developmental origins':ti,ab OR 'early-life origin':ti,ab OR 'early-life origins':ti,ab OR 'catch-up growth':ti,ab OR 'accelerated growth':ti,ab OR 'Small for Gestational Age':ti,ab OR dysmaturity:ti,ab

#2 Energy-balance related behavior

Physical acticity - Sedentary behavior - Eating behaviour

'exercise'/mj OR 'physical activity'/exp OR 'laziness'/exp OR 'lifestyle'/exp OR 'sedentary lifestyle'/exp OR 'feeding behavior'/exp OR 'health behavior'/mj OR 'childhood diet':ti,ab OR hunger:ti,ab OR hyperphagia:ti,ab OR hyperphagic:ti,ab OR 'energy expenditure':ti,ab OR 'energy level':ti,ab

No.	Embase Query 15-01-2013	Results
#13	#10 AND #11 AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [short survey]/lim)	2356
#12	#10 AND #11	2915
#11	'exercise'/mj OR 'physical activity'/exp OR 'laziness'/exp OR 'lifestyle'/exp OR 'sedentary lifestyle'/exp OR 'feeding behavior'/exp OR 'health behavior'/mj OR 'childhood diet':ab,ti OR hunger:ab,ti OR hyperphagia:ab,ti OR hyperphagic:ab,ti OR 'energy expenditure':ab,ti OR 'energy level':ab,ti	458090
#10	'birth weight'/exp OR 'prenatal exposure'/exp OR dohad:ab,ti OR 'perinatal growth':ab,ti OR 'infant growth':ab,ti OR 'intra-uterine growth':ab,ti OR 'intra-uterine programming':ab,ti OR 'developmental programming':ab,ti OR 'developmental origin':ab,ti OR 'developmental origins':ab,ti OR 'early-life origin':ab,ti OR 'early-life origins':ab,ti OR 'catch-up growth':ab,ti OR 'small for gestational age':ab,ti OR dysmaturity:ab,ti	89807

No.	Embase Query 19-05-2015	Results
#4	**#3** AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [short survey]/lim)	2879
#3	**#1** AND **#2**	3845
#2	**'exercise'**/mj OR **'physical activity'**/exp OR **'laziness'**/exp OR **'lifestyle'**/exp OR **'sedentary lifestyle'**/exp OR **'feeding behavior'**/exp OR **'health behavior'**/mj OR **'childhood diet'**:ab,ti OR **hunger**:ab,ti OR **hyperphagia**:ab,ti OR **hyperphagic**:ab,ti OR **'energy expenditure'**:ab,ti OR **'energy level'**:ab,ti	559006
#1	**'birth weight'**/exp OR **'prenatal exposure'**/exp OR **dohad**:ab,ti OR **'perinatal growth'**:ab,ti OR **'infant growth'**:ab,ti OR **'intra-uterine growth'**:ab,ti OR **'intra-uterine programming'**:ab,ti OR **'developmental programming'**:ab,ti OR **'developmental origin'**:ab,ti OR **'developmental origins'**:ab,ti OR **'early-life origin'**:ab,ti OR **'early-life origins'**:ab,ti OR **'catch-up growth'**:ab,ti OR **'accelerated growth'**:ab,ti OR **'small for gestational age'**:ab,ti OR **dysmaturity**:ab,ti	109366

No.	Embase Query 05-01-2016	Results
#4	**#3** AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [short survey]/lim)	3061
#3	**#1** AND **#2**	4094
#2	**'exercise'**/mj OR **'physical activity'**/exp OR **'laziness'**/exp OR **'lifestyle'**/exp OR **'sedentary lifestyle'**/exp OR **'feeding behavior'**/exp OR **'health behavior'**/mj OR **'childhood diet'**:ab,ti OR **hunger**:ab,ti OR **hyperphagia**:ab,ti OR **hyperphagic**:ab,ti OR **'energy expenditure'**:ab,ti OR **'energy level'**:ab,ti	589756
#1	**'birth weight'**/exp OR **'prenatal exposure'**/exp OR **dohad**:ab,ti OR **'perinatal growth'**:ab,ti OR **'infant growth'**:ab,ti OR **'intra-uterine growth'**:ab,ti OR **'intra-uterine programming'**:ab,ti OR **'developmental programming'**:ab,ti OR **'developmental origin'**:ab,ti OR **'developmental origins'**:ab,ti OR **'early-life origin'**:ab,ti OR **'early-life origins'**:ab,ti OR **'catch-up growth'**:ab,ti OR **'accelerated growth'**:ab,ti OR **'small for gestational age'**:ab,ti OR **dysmaturity**:ab,ti	114861

3. PsycINFO

#1 Perinatal influences/ DOHaD

DE "Birth Weight" OR DE "Perinatal Period" OR DE "Prenatal Exposure" OR DE "Prenatal Development" OR TI dohad OR AB dohad OR TI "Perinatal growth" OR TI "infant growth" OR TI "intra-uterine growth" OR TI "intra-uterine programming" OR TI "developmental programming" OR TI "developmental origin" OR TI "developmental origins" OR TI "early-life origin" OR TI "early-life origins" OR TI "catch-up growth" OR TI "accelerated growth" OR TI "Small for Gestational Age" OR TI "dysmaturity" OR AB "Perinatal growth" OR AB "infant growth" OR AB "intra-uterine growth" OR AB "intra-uterine programming" OR AB "developmental programming" OR AB "developmental origin" OR AB "developmental origins" OR AB "early-life origin" OR AB "early-life origins" OR AB "catch-up growth" OR AB "accelerated growth" OR AB "Small for GestaABonal Age" OR AB "dysmaturity"

#2 Energy-balance related behavior

Physical acticity - Sedentary behavior - Eating behaviour

DE "Exercise" OR DE "Activity Level" OR DE "Activities of Daily Living" OR DE "Motivation" OR DE "Physical Activity" OR DE "Diets" OR DE "Health Attitudes" OR DE "Lifestyle" OR DE "Active Living" OR DE "Health Behavior" OR DE "Swimming" OR DE "Sports" OR DE "Sports (Attitudes Toward)" OR DE "Motor Performance" OR DE "Jumping" OR DE "Running" OR DE "Walking" OR DE "Eating Behavior" OR DE "Binge Eating" OR DE "Appetite" OR DE "Eating Attitudes" OR DE "Food Intake" OR DE "Mealtimes" OR TI sedentar* OR TI satiety OR TI hunger OR TI hyperphagia OR TI hyperphagic OR TI "energy expenditure" OR TI "energy level" OR AB sedentar* OR AB satiety OR AB hunger OR AB hyperphagia OR AB hyperphagic OR AB "energy expenditure" OR AB "energy level"

#3 Publication types filter:
Limiters - Publication Type: All Journals, Peer Reviewed Journal, Peer-Reviewed Status-Unknown; Document Type: Journal Article Search modes - Boolean/Phrase

#	PsycINFO Query	Limiters/Expanders	Results
S3	(S1 AND S2)	Limiters - Publication Type: All Journals, Peer Reviewed Journal, Peer-Reviewed Status-Unknown; Document Type: Journal Article Search modes - Boolean/Phrase	493
S2	DE "Exercise" OR DE "Activity Level" OR DE "Activities of Daily Living" OR DE "Motivation" OR DE "Physical Activity" OR DE "Diets" OR DE "Health Attitudes" OR DE "Lifestyle" OR DE "Active Living" OR DE "Health Behavior" OR DE "Swimming" OR DE "Sports" OR DE "Sports (Attitudes Toward)" OR DE "Motor Performance" OR DE "Jumping" OR DE "Running" OR DE "Walking" OR DE "Eating Behavior" OR DE "Binge Eating" OR DE "Appetite" OR DE "Eating Attitudes" OR DE "Food Intake" OR DE "Mealtimes" OR TI sedentar* OR TI satiety OR TI hunger OR TI hyperphagia OR TI hyperphagic OR TI "energy expenditure" OR TI "energy level" OR AB sedentar* OR AB satiety OR AB hunger OR AB hyperphagia OR AB hyperphagic OR AB "energy expenditure" OR AB "energy level"	Search modes - Boolean/Phrase	133,188
S1	DE "Birth Weight" OR DE "Perinatal Period" OR DE "Prenatal Exposure" OR DE "Prenatal Development" OR TI dohad OR AB dohad OR TI "Perinatal growth" OR TI "infant growth" OR TI "intra-uterine growth" OR TI "intra-uterine programming" OR TI "developmental programming" OR TI "developmental origin" OR TI "developmental origins" OR TI "early-life origin" OR TI "early-life origins" OR TI "catch-up growth" OR TI "accelerated growth" OR TI "Small for Gestational Age" OR TI "dysmaturity" OR AB "Perinatal growth" OR AB "infant growth" OR AB "intra-uterine growth" OR AB "intra-uterine programming" OR AB "developmental programming" OR AB "developmental origin" OR AB "developmental origins" OR AB "early-life origin" OR AB "early-life origins" OR AB "catch-up growth" OR AB "accelerated growth" OR AB "Small for GestaABonal Age" OR AB "dysmaturity"	Search modes - Boolean/Phrase	11,705

#	PsycINFO Query 03-07-2014	Limiters/Expanders	Results
S3	S1 AND S2	Limiters - Publication Type: All Journals, Peer Reviewed Journal, Peer-Reviewed Status-Unknown; Document Type: Journal Article Search modes - Boolean/ Phrase	527
S2	DE "Exercise" OR DE "Activity Level" OR DE "Activities of Daily Living" OR DE "Motivation" OR DE "Physical Activity" OR DE "Diets" OR DE "Health Attitudes" OR DE "Lifestyle" OR DE "Active Living" OR DE "Health Behavior" OR DE "Swimming" OR DE "Sports" OR DE "Sports (Attitudes Toward)" OR DE "Motor Performance" OR DE "Jumping" OR DE "Running" OR DE "Walking" OR DE "Eating Behavior" OR DE "Binge Eating" OR DE "Appetite" OR DE "Eating Attitudes" OR DE "Food Intake" OR DE "Mealtimes" OR TI sedentar* OR TI satiety OR TI hunger OR TI hyperphagia OR TI hyperphagic OR TI "energy expenditure" OR TI "energy level" OR AB sedentar* OR AB satiety OR AB hunger OR AB hyperphagia OR AB hyperphagic OR AB "energy expenditure" OR AB "energy level"	Search modes - Boolean/ Phrase	150,128
S1	DE "Birth Weight" OR DE "Perinatal Period" OR DE "Prenatal Exposure" OR DE "Prenatal Development" OR TI dohad OR AB dohad OR TI "Perinatal growth" OR TI "infant growth" OR TI "intra-uterine growth" OR TI "intra-uterine programming" OR TI "developmental programming" OR TI "developmental origin" OR TI "developmental origins" OR TI "early-life origin" OR TI "early-life origins" OR TI "catch-up growth" OR TI "accelerated growth" OR TI "Small for Gestational Age" OR TI "dysmaturity" OR AB "Perinatal growth" OR AB "infant growth" OR AB "intra-uterine growth" OR AB "intra-uterine programming" OR AB "developmental programming" OR AB "developmental origin" OR AB "developmental origins" OR AB "early-life origin" OR AB "early-life origins" OR AB "catch-up growth" OR AB "accelerated growth" OR AB "Small for GestaABonal Age" OR AB "dysmaturity"	Search modes - Boolean/ Phrase	12,832

#	PsycINFO Query	Limiters/Expanders	Results
S3	S1 AND S2	Limiters - Publication Type: All Journals, Peer Reviewed Journal, Peer-Reviewed Status-Unknown; Document Type: Journal Article Search modes - Boolean/ Phrase	548
S2	DE "Exercise" OR DE "Activity Level" OR DE "Activities of Daily Living" OR DE "Motivation" OR DE "Physical Activity" OR DE "Diets" OR DE "Health Attitudes" OR DE "Lifestyle" OR DE "Active Living" OR DE "Health Behavior" OR DE "Swimming" OR DE "Sports" OR DE "Sports (Attitudes Toward)" OR DE "Motor Performance" OR DE "Jumping" OR DE "Running" OR DE "Walking" OR DE "Eating Behavior" OR DE "Binge Eating" OR DE "Appetite" OR DE "Eating Attitudes" OR DE "Food Intake" OR DE "Mealtimes" OR TI sedentar* OR TI satiety OR TI hunger OR TI hyperphagia OR TI hyperphagic OR TI "energy expenditure" OR TI "energy level" OR AB sedentar* OR AB satiety OR AB hunger OR AB hyperphagia OR AB hyperphagic OR AB "energy expenditure" OR AB "energy level"	Search modes - Boolean/ Phrase	161,474
S1	DE "Birth Weight" OR DE "Perinatal Period" OR DE "Prenatal Exposure" OR DE "Prenatal Development" OR TI dohad OR AB dohad OR TI "Perinatal growth" OR TI "infant growth" OR TI "intra-uterine growth" OR TI "intra-uterine programming" OR TI "developmental programming" OR TI "developmental origin" OR TI "developmental origins" OR TI "early-life origin" OR TI "early-life origins" OR TI "catch-up growth" OR TI "accelerated growth" OR TI "Small for Gestational Age" OR TI "dysmaturity" OR AB "Perinatal growth" OR AB "infant growth" OR AB "intra-uterine growth" OR AB "intra-uterine programming" OR AB "developmental programming" OR AB "developmental origin" OR AB "developmental origins" OR AB "early-life origin" OR AB "early-life origins" OR AB "catch-up growth" OR AB "accelerated growth" OR AB "Small for GestaABonal Age" OR AB "dysmaturity"	Search modes - Boolean/ Phrase	13,497

#	Query	Limiters/Expanders	Results
S3	S1 AND S2	Limiters - Publication Type: All Journals, Peer Reviewed Journal, Peer-Reviewed Status-Unknown; Document Type: Journal Article Search modes - Boolean/Phrase	577
S2	DE "Exercise" OR DE "Activity Level" OR DE "Activities of Daily Living" OR DE "Motivation" OR DE "Physical Activity" OR DE "Diets" OR DE "Health Attitudes" OR DE "Lifestyle" OR DE "Active Living" OR DE "Health Behavior" OR DE "Swimming" OR DE "Sports" OR DE "Sports #Attitudes Toward#" OR DE "Motor Performance" OR DE "Jumping" OR DE "Running" OR DE "Walking" OR DE "Eating Behavior" OR DE "Binge Eating" OR DE "Appetite" OR DE "Eating Attitudes" OR DE "Food Intake" OR DE "Mealtimes" OR TI sedentar* OR TI satiety OR TI hunger OR TI hyperphagia OR TI hyperphagic OR TI "energy expenditure" OR TI "energy level" OR AB sedentar* OR AB satiety OR AB hunger OR AB hyperphagia OR AB hyperphagic OR AB "energy expenditure" OR AB "energy level"	Search modes - Boolean/Phrase	170,849
S1	DE "Birth Weight" OR DE "Perinatal Period" OR DE "Prenatal Exposure" OR DE "Prenatal Development" OR TI dohad OR AB dohad OR TI "Perinatal growth" OR TI "infant growth" OR TI "intra-uterine growth" OR TI "intra-uterine programming" OR TI "developmental programming" OR TI "developmental origin" OR TI "developmental origins" OR TI "early-life origin" OR TI "early-life origins" OR TI "catch-up growth" OR TI "accelerated growth" OR TI "Small for Gestational Age" OR TI "dysmaturity" OR AB "Perinatal growth" OR AB "infant growth" OR AB "intra-uterine growth" OR AB "intra-uterine programming" OR AB "developmental programming" OR AB "developmental origin" OR AB "developmental origins" OR AB "early-life origin" OR AB "early-life origins" OR AB "catch-up growth" OR AB "accelerated growth" OR AB "Small for GestaABonal Age" OR AB "dysmaturity"	Search modes - Boolean/Phrase	14,068

4. Cochrane

#1 Perinatal influences/ DOHaD

Birth weight OR "Prenatal Exposure" OR dohad OR "Perinatal" OR "infant growth" OR "intra-uterine growth" OR "infant programming" OR "fetal programming" OR "intra-uterine programming" OR "developmental programming" OR "intra-uterine plasticity" OR "developmental plasticity" OR "developmental origin" OR "developmental origins" OR "early-life origin" OR "early-life origins" OR "catch-up growth" OR "Small for Gestational Age" OR dysmaturity OR "accelerated growth"

#2 Energy-balance related behavior

Physical acticity - Sedentary behavior - Eating behaviour

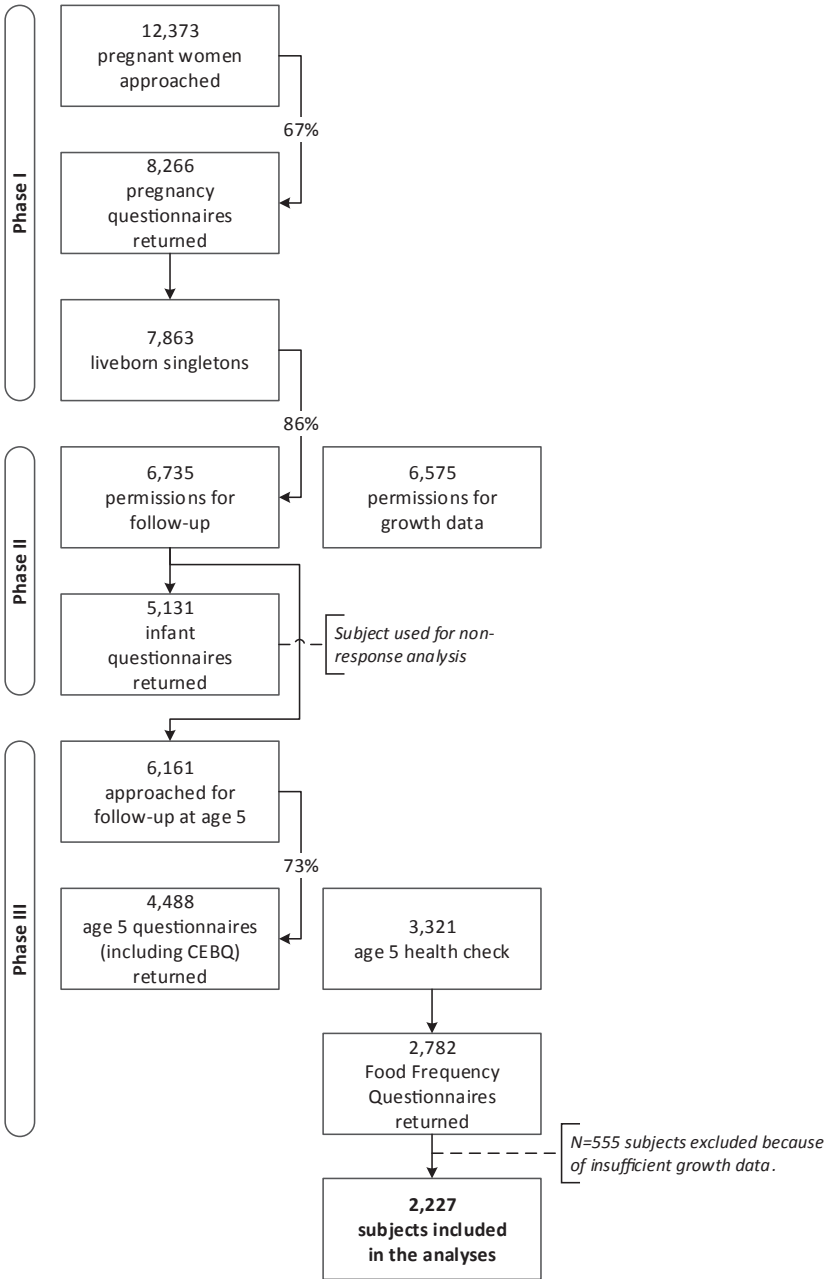
"Running" OR "Swimming" OR "Walking" OR "Sports" OR "Life Style" OR "Sedentary Lifestyle" OR "Appetite" OR "Health Behavior" OR "Feeding Behavior" OR "physical activity" OR appetit* OR satiety OR "childhood diet" OR sport* OR exercise* OR "activity level" OR "motor activity" OR "locomotor activity" OR "sedentary" OR sedentarism OR sedentariness OR "physical inactivity" OR "sitting" OR "diet behavior" OR "dietary behavior" OR "feeding behavior" OR "appetitive behavior" OR "diet behaviour" OR "dietary behaviour" OR "feeding behaviour" OR "appetitive behaviour" OR "diet preference" OR "diet preferences" OR "dietary preference" OR "dietary preferences" OR "feeding preference" OR "feeding preferences" OR "feeding practice" OR "feeding practices" OR "diet regulation" OR "feeding regulation" OR "diet control" OR "dietary control" OR "feeding control" OR hunger OR hyperphagia OR hyperphagic OR "energy expenditure" OR "energy level"

ID	Date Run: 03/07/14 11:39:10.627	Hits
#1	Birth weight or "Prenatal Exposure" or dohad or "Perinatal" or "infant growth" or "intra-uterine growth" or "infant programming" or "fetal programming" or "intra-uterine programming" or "developmental programming" or "intra-uterine plasticity" or "developmental plasticity" or "developmental origin" or "developmental origins" or "early-life origin" or "early-life origins" or "catch-up growth" or "Small for Gestational Age" or dysmaturity or "accelerated growth":ti,ab,kw (Word variations have been searched)	7966
#2	"Running" or "Swimming" or "Walking" or "Sports" or "Life Style" or "Sedentary Lifestyle" or "Appetite" or "Health Behavior" or "Feeding Behavior" or "physical activity" or appetit* or satiety or "childhood diet" or sport* or exercise* or "activity level" or "motor activity" or "locomotor activity" or "sedentary" or sedentarism or sedentariness or "physical inactivity" or "sitting" or "diet behavior" or "dietary behavior" or "feeding behavior" or "appetitive behavior" or "diet behaviour" or "dietary behaviour" or "feeding behaviour" or "appetitive behaviour" or "diet preference" or "diet preferences" or "dietary preference" or "dietary preferences" or "feeding preference" or "feeding preferences" or "feeding practice" or "feeding practices" or "diet regulation" or "feeding regulation" or "diet control" or "dietary control" or "feeding control" or hunger or hyperphagia or hyperphagic or "energy expenditure" or "energy level":ti,ab,kw (Word variations have been searched)	68198
#3	#1 and #2	402

ID	Date Run: 19/05/15 12:18:28.74	Hits
#1	Birth weight or "Prenatal Exposure" or dohad or "Perinatal" or "infant growth" or "intra-uterine growth" or "infant programming" or "fetal programming" or "intra-uterine programming" or "developmental programming" or "intra-uterine plasticity" or "developmental plasticity" or "developmental origin" or "developmental origins" or "early-life origin" or "early-life origins" or "catch-up growth" or "Small for Gestational Age" or dysmaturity or "accelerated growth":ti,ab,kw (Word variations have been searched)	8890
#2	"Running" or "Swimming" or "Walking" or "Sports" or "Life Style" or "Sedentary Lifestyle" or "Appetite" or "Health Behavior" or "Feeding Behavior" or "physical activity" or appetit* or satiety or "childhood diet" or sport* or exercise* or "activity level" or "motor activity" or "locomotor activity" or "sedentary" or sedentarism or sedentariness or "physical inactivity" or "sitting" or "diet behavior" or "dietary behavior" or "feeding behavior" or "appetitive behavior" or "diet behaviour" or "dietary behaviour" or "feeding behaviour" or "appetitive behaviour" or "diet preference" or "diet preferences" or "dietary preference" or "dietary preferences" or "feeding preference" or "feeding preferences" or "feeding practice" or "feeding practices" or "diet regulation" or "feeding regulation" or "diet control" or "dietary control" or "feeding control" or hunger or hyperphagia or hyperphagic or "energy expenditure" or "energy level":ti,ab,kw (Word variations have been searched)	76603
#3	#1 and #2	482

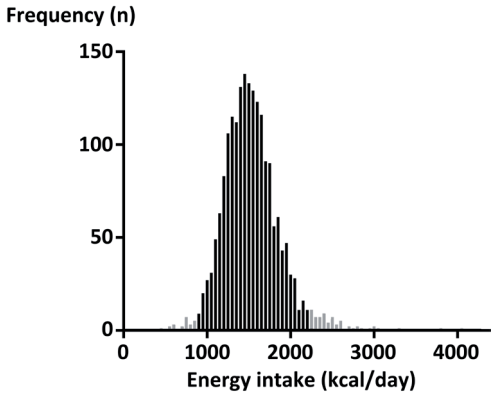
ID	Date Run: 05/01/16 14:45:21.756	HIts
#1	Birth weight or "Prenatal Exposure" or dohad or "Perinatal" or "infant growth" or "intra-uterine growth" or "infant programming" or "fetal programming" or "intra-uterine programming" or "developmental programming" or "intra-uterine plasticity" or "developmental plasticity" or "developmental origin" or "developmental origins" or "early-life origin" or "early-life origins" or "catch-up growth" or "Small for Gestational Age" or dysmaturity or "accelerated growth":ti,ab,kw (Word variations have been searched)	9571
#2	"Running" or "Swimming" or "Walking" or "Sports" or "Life Style" or "Sedentary Lifestyle" or "Appetite" or "Health Behavior" or "Feeding Behavior" or "physical activity" or appetit* or satiety or "childhood diet" or sport* or exercise* or "activity level" or "motor activity" or "locomotor activity" or "sedentary" or sedentarism or sedentariness or "physical inactivity" or "sitting" or "diet behavior" or "dietary behavior" or "feeding behavior" or "appetitive behavior" or "diet behaviour" or "dietary behaviour" or "feeding behaviour" or "appetitive behaviour" or "diet preference" or "diet preferences" or "dietary preference" or "dietary preferences" or "feeding preference" or "feeding preferences" or "feeding practice" or "feeding practices" or "diet regulation" or "feeding regulation" or "diet control" or "dietary control" or "feeding control" or hunger or hyperphagia or hyperphagic or "energy expenditure" or "energy level":ti,ab,kw (Word variations have been searched)	83424
#3	#1 and #2	545

SUPPLEMENTARY FIGURE S5.1. SAMPLING PROCEDURE OF THE ABCD STUDY.



Supplementary Figure S5.1 Flowchart of the sampling procedure of the ABCD cohort and selection of subjects included in this study.

SUPPLEMENTARY FIGURE S5.2. HISTOGRAM SHOWING THE REPORTED MEAN DAILY ENERGY INTAKE.



Supplementary Figure S5.2 Histogram of the distribution of the parent-reported mean daily energy intake in our cohort. In gray are the values more than +2SD above the mean or less than -2SD below the mean, which are excluded in the sensitivity analysis of supplementary table 1.

SUPPLEMENTARY TABLE S5.1. SENSITIVITY ANALYSIS WITH THE EXCLUSION OF EXTREME ENERGY INTAKE VALUES.

	Energy intake (kcal/day) B (95%-CI)	**Standard. Beta (95%-CI)**	**P-value**
Weight			
Birth weight	-2.7 (-23.5; 18.0)	-0.01 (-0.07; 0.05)	0.80
Conditional weight 0 – 1 mo.	0.01 (-17.9; 17.9)	0.00 (-0.04; 0.04)	1.00
Conditional weight 1 – 3 mo.	28.4 (6.7; 50.1)	0.09 (0.02; 0.15)	0.01
Conditional weight 3 – 6 mo.	25.1 (5.7; 44.5)	0.07 (0.02; 0.13)	0.02
Conditional weight 6 – 12 mo.	6.4 (-13.8; 26.7)	0.02 (-0.05; 0.09)	0.54
Conditional weight 12 mo. – 5 y.	65.9 (22.4; 109.4)	0.19 (0.06; 0.32)	0.02
Height			
Conditional height 0 – 1 mo.	-26.5 (-48.1; -2.4)	-0.08 (-0.15; -0.01)	0.02
Conditional height 1 – 3 mo.	-36.9 (-62.4; -11.4)	-0.12 (-0.20; -0.04)	0.005
Conditional height 3 – 6 mo.	-8.4 (-31.3; 14.5)	-0.03 (-0.10; 0.05)	0.47
Conditional height 6 – 12 mo.	-6.8 (-30.8; 17.3)	-0.02 (-0.10; 0.06)	0.58
Conditional height 12 mo. – 5 y.	-38.3 (-76.6; 0.06)	-0.11 (-0.23; 0.00)	0.05

Supplementary Table S5.1 Results of the sensitivity analysis of the association of birth weight, conditional weight and conditional height (all in Z-scores) with mean daily energy intake at age 5, with outcome values more than +2SD above the mean or less than -2SD below the mean excluded. The coefficients are presented both in the original units of measurement and in standardized betas. Analysis adjusted for sex, gestational age, ethnicity, maternal and paternal BMI, socio-economic status, smoking during pregnancy, duration of exclusive breastfeeding, current age, height and BMI, screen time and PA score at age 5.

SUPPLEMENTARY TABLE S5.2 SENSITIVITY ANALYSIS WITH THE EXCLUSION OF CHILDREN BORN PRETERM AND/OR WITH LOW BIRTH WEIGHT.

	Energy intake (kcal/day) B (95%-CI)	Standard. Beta (95%-CI)	P-value	Satiety Response (score) B (95%-CI)	Standard. Beta (95%-CI)	P-value
Weight						
Birth weight	-5.9 (-30.2; 18.4)	-0.02 (0.09; 0.05)	0.63	-0.02 (-0.05; 0.01)	-0.04 (-0.10; 0.02)	0.28
Conditional weight 0 – 1 mo.	5.4 (-15.4; 26.2)	0.01 (-0.03; 0.06)	0.61	-0.03 (-0.06; -0.00)	-0.06 (-0.12; -0.01)	0.03
Conditional weight 1 – 3 mo.	30.8 (5.5; 56.0)	0.09 (0.02; 0.17)	0.02	-0.05 (-0.08; -0.02)	-0.08 (-0.13; -0.03)	0.003
Conditional weight 3 – 6 mo.	24.4 (2.1; 46.6)	0.07 (0.01; 0.14)	0.03	-0.04 (-0.07; -0.01)	-0.07 (-0.12; -0.02)	0.007
Conditional weight 6 – 12 mo.	10.3 (-13.2; 33.9)	0.03 (-0.04; 0.11)	0.39	-0.08 (-0.11; -0.05)	-0.17 (-0.24; -0.11)	<0.001
Conditional weight 12 mo. – 5 y.	84.3 (33.9; 134.7)	0.24 (0.10; 0.39)	0.001	-0.13 (-0.20; -0.07)	-0.25 (-0.38; -0.13)	<0.001
Height						
Conditional height 0 – 1 mo.	-41.7 (-66.4; -17.0)	-0.13 (-0.21; -0.05)	<0.001	0.01 (-0.02; 0.03)	-0.00 (-0.00; 0.00)	0.61
Conditional height 1 – 3 mo.	-34.8 (-58.2; -11.4)	0.11 (-0.18; -0.04)	0.004	-0.00 (-0.03; 0.02)	-0.02 (-0.60; 0.40)	0.74
Conditional height 3 – 6 mo.	-7.4 (-28.6; 13.7)	-0.02 (-0.10; 0.05)	0.49	-0.03 (-0.05; 0.00)	-0.09 (-0.15; -0.00)	0.04
Conditional height 6 – 12 mo.	-10.7 (-32.7; 11.4)	-0.03 (-0.10; 0.04)	0.34	-0.02 (-0.05; 0.003)	-0.04 (-0.10; 0.01)	0.09
Conditional height 12 mo. – 5 y.	-36.1 (-71.2; -0.97)	-0.11 (-0.21; 0.00)	0.04	-0.02 (-0.06; 0.01)	-0.04 (-0.12; 0.02)	0.15

Supplementary Table S5.2 Results of the sensitivity analysis of the association of birth weight, conditional weight and conditional height (all in Z-scores) with mean daily energy intake and satiety response at age 5, with children born preterm (<37 weeks of gestation) and/or with low birth weight (birth weight more than -2SD below the mean) excluded. The coefficients are presented both in the original units of measurement and in standardized betas. Analysis adjusted for sex, gestational age, ethnicity, maternal and paternal BMI, socio-economic status, smoking during pregnancy, duration of exclusive breastfeeding, current age, height and BMI, screen time and PA score at age 5.

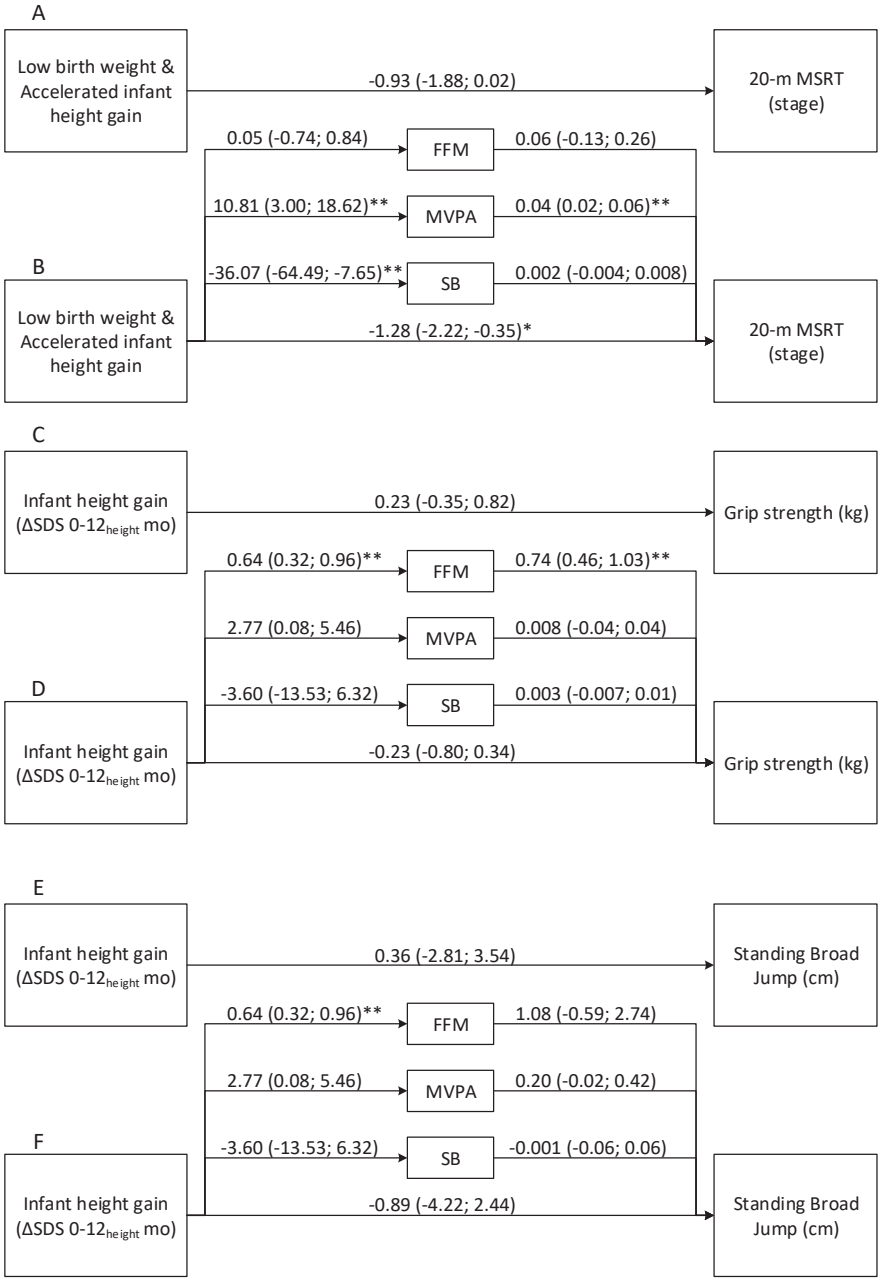
SUPPLEMENTARY TABLE S6.1 EXTENDED OVERVIEW OF THE ASSOCIATIONS OF BIRTH WEIGHT AND INFANT GROWTH WITH MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR.

			MVPA (min/day)		SB (min/day)	
			β-coefficient (95%-CI)	P-value	β-coefficient (95%-CI)	P-value
Birth weight (SD) n = 183		**Model 1**	-1.1 (-2.9; 0.8)	0.26	1.9 (-3.6; 7.4)	0.49
		Model 2	-		-	
		Model 3	-1.0 (-3.1; 1.0)	0.31	2.9 (-2.7; 8.5)	0.31
Infant weight gain (ΔSDS) n = 183	**0-24 months**	**Model 1**	-0.8 (-2.7; 1.1)	0.41	5.6 (0.8; 10.4)	0.07
		Model 2	-2.5 (-5.3; 0.3)	0.08	11.6 (3.5; 19.8)	<0.01
		Model 3	-1.5 (-4.5; 1.5)	0.34	11.9 (2.2; 21.7)	0.02
	0-12 months	**Model 1**	-0.8 (-2.8; 1.3)	0.46	14.4 (4.8; 24.0)	0.04
		Model 2	-2.9 (-8.3; 2.5)	0.29	20.1 (4.6; 35.8)	<0.01
		Model 3	2.3 (-2.7; 7.3)	0.37	19.5 (3.2; 35.8)	0.02
	12-24 months	**Model 1**	-0.7 (-5.4; 4.1)	0.78	4.2 (-1.8; 10.2)	0.17
		Model 2	-2.1 (-7.4; 3.2)	0.44	7.6 (-1.1; 16.2)	0.09
		Model 3	1.5 (-3.2; 6.2)	0.52	6.0 (-3.6; 15.6)	0.22
Infant height gain (ΔSDS) n = 133	**0-24 months**	**Model 1**	1.1 (-1.1; 3.3)	0.32	1.6 (-5.0; 8.2)	0.63
		Model 2	1.0 (-1.8; 3.7)	0.49	1.6 (-6.4; 9.6)	0.70
		Model 3	3.0 (0.4; 5.6)	0.02	0.9 (-8.0; 9.8)	0.84
	0-12 months	**Model 1**	1.9 (-0.4; 4.4)	0.11	-1.4 (-8.8; 5.9)	0.70
		Model 2	1.8 (-1.1; 4.7)	0.22	-2.5 (-11.1; 6.2)	0.57
		Model 3	2.9 (0.2; 5.6)	0.04	-3.9 (-13.3; 6.2)	0.71
	12-24 months	**Model 1**	-1.4 (-5.0; 2.3)	0.46	7.8 (-3.2; 18.8)	0.16
		Model 2	-0.9; -5.0; 3.2)	0.67	7.6 (-4.5; 19.7)	0.22
		Model 3	1.9 (-1.6; 5.5)	0.29	6.3 (-5.9; 18.5)	0.31

			MVPA (min/day)		SB (min/day)	
			β-coefficient (95%-CI)	P-value	β-coefficient (95%-CI)	P-value
Infant BMI gain (ΔSDS) n = 133	**0-24 months**	**Model 1**	-1.4 (-3.1; 0.4)	0.13	7.3 (2.0; 12.6)	<0.01
		Model 2	-1.8 (-3.7; 0.2)	0.07	7.5 (1.9; 13.2)	<0.01
		Model 3	-1.0 (-3.1; 1.2)	0.38	6.0 (0.4; 11.6)	0.03
	0-12 months	**Model 1**	-1.9 (-3.9; 0.1)	0.06	8.6 (2.8; 14.5)	<0.01
		Model 2	-2.3 (-4.4; -0.1)	0.04	7.9 (1.5; 14.3)	0.01
		Model 3	-0.3 (-2.2; 1.7)	0.78	6.4 (0.7; 12.1)	0.03
	12-24 months	**Model 1**	0.7 (-2.5; 3.9)	0.66	0.5 (-9.2; 10.3)	0.92
		Model 2	-0.3 (-3.8; 3.2)	0.86	5.5 (-4.6; 15.7)	0.29
		Model 3	0.6 (-2.4; 3.6)	0.69	4.1 (-5.8; 14.0)	0.41

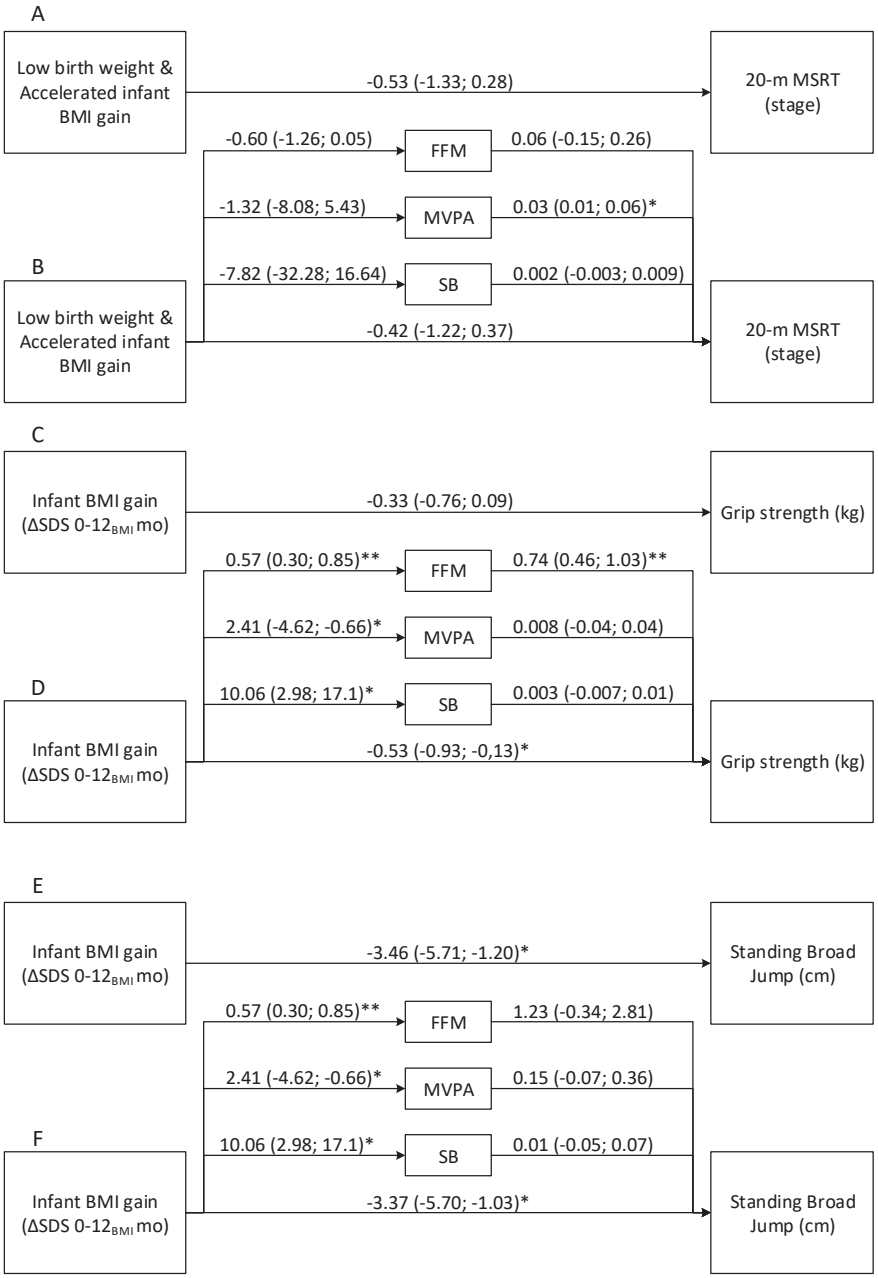
Supplementary table S6.1 Association of birth weight (SD) and different periods of infant weight, height and body mass index gain with time in moderate-to-vigorous physical activity and sedentary behavior. Model 1: Univariate analysis. Model 2: Growth parameter adjusted for birth weight (all analyses), prior growth (for the 12 to 24 month period), and concurrent height gain (for infant weight gain). Model 3: Model 2 additionally adjusted for sex, gestational age, current age, socio-economic status, maternal age, mean daily wear time, accelerometer wear date, and analyses of MVPA adjusted for time in SB and analyses of SB adjusted for time in MVPA. Abbreviations: MVPA – Moderate-to-vigorous physical activity; SB – Sedentary Behavior; ΔSDS – change in SD score; BMI – Body mass index.

SUPPLEMENTARY FIGURE S7.1. MEDIATION ANALYSIS OF FAT-FREE MASS, MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR ON THE ASSOCIATION OF INFANT HEIGHT GAIN WITH PHYSICAL FITNESS.



Supplementary figure S7.1 A. Total effect (regression coefficient with 95% confidence interval in parenthesis) of low birth weight and accelerated infant height gain on the 20 meter multistage shuttle run test, compared to the other birth weight/infant height gain categories combined. **B.** Results of the mediation analysis, showing the direct effect of low birth weight and accelerated infant height gain on the 20 meter multistage shuttle run test, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior. **C. & E.** Individual total effects of birth weight and infant height gain on hand grip strength and standing broad jump, respectively. **D. & F.** Results of the mediation analyses showing the direct effect of birth weight and infant height gain, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior, on hand grip strength and standing broad jump, respectively. Analysis adjusted for sex, gestational age, current age, socio-economic status, parental height and BMI, duration of exclusive breast feeding and smoking during pregnancy. The analyses for 20 meter multistage shuttle run test and standing broad jump test are further adjusted for current height, weight and BMI. Of note, small differences in regression coefficients from those in table 3 are the result of the exclusion of 11 subjects due to missing accelerometry data. *P<0.01, **P<0.001. Abbreviations: 20-m MSRT – 20 meter multistage shuttle run test; FFM – fat-free mass; MVPA – moderate-to-vigorous physical activity; SB – Sedentary Behavior.

SUPPLEMENTARY FIGURE S7.2. MEDIATION ANALYSIS OF FAT-FREE MASS, MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR ON THE ASSOCIATION OF INFANT BMI GAIN WITH PHYSICAL FITNESS.



Supplementary figure S7.2. A. Total effect (regression coefficient with 95% confidence interval in parenthesis) of low birth weight and accelerated infant BMI gain on the 20 meter multistage shuttle run test, compared to the other birth weight/infant BMI gain categories combined. **B.** Results of the mediation analysis, showing the direct effect of low birth weight and accelerated infant BMI gain on the 20 meter multistage shuttle run test, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior. **C. & E.** Individual total effects of birth weight and infant BMI gain on hand grip strength and standing broad jump, respectively. **B. & F.** Results of the mediation analyses showing the direct effect of birth weight and infant BMI gain, and the mediation effects of fat-free mass, moderate-to-vigorous physical activity and sedentary behavior, on hand grip strength and standing broad jump, respectively. Analysis adjusted for sex, gestational age, current age, socio-economic status, parental height and BMI, duration of exclusive breast feeding and smoking during pregnancy. The analyses for 20 meter multistage shuttle run test and standing broad jump test are further adjusted for current height, weight and BMI. Of note, small differences in regression coefficients from those in table 3 are the result of the exclusion of 11 subjects due to missing accelerometry data. *P<0.01, **P<0.001. Abbreviations: 20-m MSRT – 20 meter multistage shuttle run test; FFM – fat-free mass; MVPA – moderate-to-vigorous physical activity; SB – Sedentary Behavior

SUPPLEMENTARY TABLE S8.1 CHARACTERISTICS OF THE POTENTIAL CONFOUNDING VARIABLES

	Characteristics of data collection		Characteristics of data handling		
	Method of collection	**Child's age at collection**	**Unit of measurement**	**Scale of measurement**	**Denomination of categories (where appropriate)**
Gestational age	Obtained from Youth Health Care	Birth	Weeks	Continuous	-
Sex	Obtained from Youth Health Care	Birth	-	Dichotomous	Male; Female.
Current age	Obtained during 'age 5 health check'	5-6 years	Years	Continuous	-
Current height	Obtained during 'age 5 health check'	5-6 years	Centimeters	Continuous	-
Current BMI	Obtained during 'age 5 health check'	5-6 years	Kg/m^2	Continuous	-
Socio-economic status	Obtained from maternal questionnaire	Prenatally	Maternal education	Categorical	Low (defined as no or primary school education; lower vocational secondary education or technical secondary education); Mid (higher vocational secondary education or intermediate vocational education); High (higher vocational education, university education).
Ethnicity	Obtained from maternal questionnaire	Prenatally	Maternal country of birth	Categorical	Dutch; Moroccan; Surinamese; Turkish; Other.
Maternal pre-pregnancy BMI	Obtained from maternal questionnaire	Prenatally	Kg/m^2	Continuous	-
Maternal smoking during pregnancy	Obtained from maternal questionnaire	Prenatally	-	Categorical	Yes (defined as at least one cigarette per day); No.

	Characteristics of data collection		Characteristics of data handling		
	Method of collection	**Child's age at collection**	**Unit of measurement**	**Scale of measurement**	**Denomination of categories (where appropriate)**
Maternal alcohol intake during pregnancy	Obtained from maternal questionnaire	Prenatally	-	Categorical	Yes (defined as at least one unit of alcohol per day); No.
Maternal physical activity during pregnancy	Obtained from maternal questionnaire	Prenatally	Minutes per day leisure time physical activity	Continuous	

Supplementary table S8.1 Characteristics of the variables the statistical models are adjusted for, including the method and timing of data collection and how the variables are adjusted for in the analyses.

SUPPLEMENTARY TABLE S8.2 ASSOCIATION OF PEP AND RSA WITH ENERGY BALANCE-RELATED BEHAVIOR (B-PATH)

		Mean daily energy intake (kcal/day)	Satiety response (Score)	PA level (min/day)	Screen time (min/day)
Pre-ejection period	(B1 path)	1.46 (-1.13; 4.06)	-0.001 (-0.006; 0.003)	-0.05 (-0.68; 0.67)	-0.23 (-0.62; 0.15)
Respiratory sinus arrhythmia	(B2 path)	-0.22 (-0.67; 0.23)	-0.0002 (-0.0010; 0008)	-0.04 (-0.12; 0.09)	0.04 (-0.04; 0.10)

Supplementary table S8.2 Associations (β-coefficients and 95% confidence intervals (95%-CI)) of pre-ejection period and respiratory sinus arrhythmia with mean daily energy intake, satiety response, PA level and screen time (B path in figure 8.2), adjusted for gestational age, sex, current age, current height, current BMI, socioeconomic status, ethnicity, maternal pre-pregnancy BMI, and maternal smoking, alcohol intake, folic acid intake and physical activity level during pregnancy.

SUPPLEMENTARY TABLE S8.3. RESULTS OF THE SENSITIVITY ANALYSIS FOR UNMEASURED MEDIATOR-OUTCOME CONFOUNDING

(a) Sensitivity analysis for unmeasured mediator-outcome confounding of the direct effect of conditional height on mean daily energy intake.

γ_m (SD)	δ_m (kcal/day)
0	∞
0.2	-96.40
0.25	-77.12
0.4	-48.20
0.5	-38.56
0.6	-32.13
0.75	-25.71
0.8	-24.10
1	-19.28

(b) Sensitivity analysis for unmeasured mediator-outcome confounding of the direct effect of conditional weight on screen time.

γ_m (SD)	δ_m (min/day)
0	∞
0.2	21.50
0.25	17.20
0.4	10.75
0.5	8.60
0.6	7.17
0.75	5.73
0.8	5.38
1	4.30

Supplementary table S8.3 Results of the sensitivity analysis for unmeasured mediator-outcome confounding of the direct effect of conditional height on mean daily energy intake (upper table) and the direct effect of conditional weight on screen time (lower table). γm is defined as the difference in means of the unmeasured confounder associated with a one unit difference in independent variable. δm is defined as the corresponding direct effect of the unmeasured confounder on the dependent variable necessary to reduce the direct effect estimate to the null.

DANKWOORD

DANKWOORD

Het is mooi om te zien hoeveel fijne mensen er voor je klaarstaan tijdens je promotieonderzoek. Hieronder slechts een greep van alle mensen die klaarstonden tijdens de mijne.

Allereerst alle kinderen van de ABCD studie, en hun ouders. In het bijzonder Abel, Alexander, Aline, Anke, Anna, Anna, Anne, Annika, Antonia, Antony, Bernd, Boaz, Bonni, Bram, Brechtje, Brechtje, Britt, Cato, Cenna, Charissa, Chloé, Claudio, Cléo, Corinne, Daan, Dani, Demi, Dennis, Dora, Duco, Elin, Emma, Emma, Emma, Emma, Erik, Eva, Eva, Eva, Faas, Faas, Fauve, Fay, Felix, Femke, Fien, Fiene, Fleur, Florine, Floris, Francisca, Frans, Fy, Gosewijn, Gwendolyn, Hanne, Holly, Hugo, Hugo, Inez, Ione, Iris, Isa, Isa, Isis, Jada, Jasmijn, Jeen, Jelle, Jesse, Jesse, Jip, Joeri, Jonathan, Joost, Joris, Joris, Jort, Julia, Julian, Julian, Juliette, Julius, Jurriaan, Just, Kamiel, Kelsey, Kick, Koen, Koos, Kyran, Lance, Leah, Lente, Léon, Levi, Levi, Liam, Liese, Lila, Lisa, Lisa, Liv, Liv, Liza, Loes, Loïs, Lotte, Lotus, Luca, Luca, Luka, Luka, Luke, Lynn, Maarten, Mae, Mara, Mare, Maren, Maria, Maria, Mark, Mats, Mats, Maud, Max, Medoune, Mees, Mick, Miguel, Mika, Mika, Milan, Milan, Milan, Milan, Milos, Morris, Naomi, Nena, Niek, Niels, Noor, Noortje, Omar, Ophelie, Pepijn, Philip, Phyline, Pien, Pim, Ploon, Quinten, Rens, Renske, Roan, Robbin, Robin, Roemer, Roman, Roman, Roshil, Ruby, Ruud, Salahdin, Sam, Sanne, Sara, Sikko, Silke, Sjoerd, Sjoerd, Sophie, Sophie, Soumia, Sterre, Thibault, Thijmen, Tijn, Tijs, Tobias, Tom, Tomas, Twan, Tymen, Viggo, Ward, Watze, Yaell, Yannick, Yvette, Zeger en Zeno. Ofwel, de 194 kleine helden die op veelal regenachtige herfstdagen in 2012 naar het Olympisch Stadion zijn gekomen om mee te doen aan het extra meetmoment. Dank dat jullie er waren. Zonder jullie wás er niets te onderzoeken.

Maar jullie waren er wel; in grote getalen! Dus ik ben ook veel dank verschuldigd aan alle vrijwilligers die mij hebben geholpen met het uitvoeren van de metingen. Een onmisbaar team van studenten: Susan de Swart, Gerben Vermeulen, Lindy van Dorp, Djamilla van der Stap, Petra Roeleveld, Simone van den Berg, Roel Janssen en Chris van Houten. Van het 'oefenen' op een basisschool tot het ophalen van de accelerometers: jullie hebben fantastisch werk verricht! Maar ook Adriëtte, Allison, Annelies, Anouk, Charlotte, Cornelia, Elise, Helene, Hester B., Hester N., Jolice, Jorn, Katja, Mai, Marieke, Merel, Monique, Patrick, Rik, Sandra, Sietske, Stefanie, Suzanne, Tamara en Willemijn: de collega's en vrienden die tijdens de meetdagen zo enthousiast meehielpen. Wat hebben jullie fantastisch mee gerend, gesprongen, gemeten en 'geknijpt'! Dank daarvoor.

Prof. dr. R.J.B.J. Gemke, Beste Reinoud, laatst vond ik de allereerste schetsen van een onderzoek die wij wilden opzetten. De datum, september 2007. Al tien jaar heb je me kansen, mogelijkheden en vertrouwen gegeven om dit onderzoek op te zetten en uit te voeren. Je hebt me gesteund en gestimuleerd om te groeien als wetenschapper. Je bent een ware mentor, en met jouw mentorschap ben ik geworden tot de eigenwijze onderzoeker die ik nu ben.

Prof. dr. M.J.M. Chin A Paw, Beste Mai, het onderzoek stond al in de stijgers toen jij er bij kwam. En jouw komst was het beste wat er voor het onderzoek kon gebeuren. Ongeëvenaarde expertise en overzicht is één ding, maar je betrokkenheid, enthousiasme en inzet om van ieder onderdeel van dit onderzoek het mooiste te maken was minstens zo waardevol. Jouw grote ambities staat laagdrempelig contact nooit in de weg: meermaals leidde een onderzoeksbespreking tot een gezellige kop koffie in het tentje op de hoek! Bedankt voor je persoonlijke aandacht.

Dr. T.G.M. Vrijkotte, Beste Tanja, je bent de ware Mater Familias van de ABCD studie, en daarmee ook van ons promovendi. En als op de jaarlijkse barbecue in jouw tuin de familie compleet was, zag je dat het goed was. Bedankt voor je inzet voor de ABCD studie en mijn 'zijproject'. Ik hoop dat nog veel jonge onderzoekers onder jouw moederlijke vleugels mogen promoveren.

De leden van de leescommissie, prof. dr. J.B. van Goedoever, prof dr. V.W. Jaddoe, prof. dr. W. van Mechelen, prof. dr. T.J. Roseboom, dr. S.A. Clur en dr. M. van Eijsden, wil ik hartelijk bedanken voor de tijd en aandacht die zij hebben besteed aan de beoordeling van mijn proefschrift. Dank ook voor uw bereidheid in mijn promotiecommissie zitting te nemen. Ik ben vereerd met uw aanwezigheid.

De directie van het Olympisch Stadion wil ik hartelijk danken voor de mogelijkheid het onderzoek in het Olympisch Stadion te organiseren. Dat stadion is hét icoon van Sport en Beweging in Nederland en was daarmee de enige juiste plek voor het onderzoek. Blijkens ook uit de vader die teleurgesteld riep toen de metingen waren afgerond: "Maar ik wil nog niet weg! Kan je niet nog meer meten?".

Alle kinderartsen en arts-assistenten met wie ik de afgelopen jaren heb samengewerkt. Dank voor de heerlijke werksfeer, interesse in mijn onderzoek en flexibiliteit als onderzoeksverplichtingen weer eens door mijn klinische taken heen fietsten. De kinderartsen uit het Spaarneziekenhuis – Peter, Marlies, Arnold, Marieke, Jan-Alle, Wendy, Herma en Nienke – wil ik bedanken voor de tijd die zij mij gaven om mijn onderzoek op te starten. Jullie zagen mijn enthousiasme en hebben me de gelegenheid gegeven

om daar iets moois mee te doen; betere opleiders kan je niet krijgen. Reinoud Gemke en Marie-José Walenkamp, mijn opleiders van het VUmc, dank ik voor hun vertrouwen en ruimte om het onderzoek naast – soms tijdens – mijn opleiding voort te kunnen zetten. Mijn huidige opleiders, de kindercardiologen van CAHAL, waaronder Nico, Irene, Sally, Ad, Bart, Lukas en Ingmar. Laatste loodjes wegen zwaar, maar jullie aanmoedigingen naar de eindstreep en enthousiasme toen het écht af was, deden veel goeds. Ik verheug me er op om mijn onderzoeksfocus te verleggen naar de kindercardiologie. Als jullie wetenschappelijke begeleiding even begenadigd is als de klinische, gaat dat helemaal goed komen. Mede-AIOSsen van weleer: Ilse en Jaap (Gouden Lichting 2010), Marc en Martijn (skicie 1.0), Marjolein, Yvette, Annemieke, Marieke, Meeike, Chris, Karlijn, Susan, Anders, Emile, Daniel en Rik (borrelbuddy's). Van Ysbreeker tot Après Ski, wat heb ik met jullie gelachen en gefeest, en wat hadden we het gezellig.

Gezellig was het ook op PK4X! Dankzij mijn buren Gerrit en Stefanie, kamergenoten Hester, Suzanne, Jolice, Marita, Kim, Monique, Charlotte, Diane, Mirjam, Dana, Raphaële, Loubna, Hannemieke, Marieke en Jan, en lunchtafelgenoten Sophie, Willemijn, Marc, Bibian, Annelies, Katja, Lindsay, Stijn, Fatma, Eline H., Sietske, Sandra, Miret, Femke, Ineke, Anneke, Eline van D., Marleen en Annemieke. Van bekvechten over de muziekkeuze in de kamer, tot slap geouwehoer aan de lunchtafel; met jullie was promoveren wél leuk.

Mede-ABCD'ers, Gerrit van den Berg, Marieke de Beer, Adriëtte Oostvogels, Noekie van Lieshout, Viyan Rashid, Sanne de Laat, Aimée van Dijk, Marieke de Hoog, Eva Loomans, Margreet Harskamp-van Ginkel, Jessica Hrudey, Laetitia Smarius en Hadi Zafarmand. Dank voor de samenwerking binnen de ABCD studie. De vergaderingen en congressen waren gezellig door jullie. Door jullie commitment en werklust was de ABCD studie een soepel rijdende trein waar ik op kon springen. Door jullie is het een prachtig cohort geworden, waar we in de toekomst nog veel moois aan gaan beleven.

Graag wil ik ook medeauteurs Prof. dr. Jos Twisk, dr. Maaike Gademan en Ilse Jansma bedanken voor het belangrijke werk dat ze hebben geleverd aan de betreffende artikelen. Jullie inzet en input was onmisbaar!

Minstens zo onmisbaar: alle lieve dames van het secretariaat. Marieke van Ojik-Werkhoven, Sylvia Brugel-Band, Manon Buskermolen en Anne Schumacher heb ik menigmaal van hun werk gehouden. Meestal kwam ik langs voor een babbel, soms voor een organisatorisch probleem. Altijd was ik welkom. Dank voor jullie aandacht en interesse. Jullie zijn goud waard.

Dr. Suat Simsek, beste Suat, als medisch student kwam ik ooit een wetenschappelijke stage bij je lopen, en moet je nou eens zien: een proefschrift! Jij hebt de onderzoekspassie in mij aangestoken, en dit boekje is meer aan jou te danken dan je denkt. Omdat ik zo nodig kinderarts moest worden, zijn onze onderzoekswegen gescheiden, en dat ik vind ik jammer. Je blijft altijd een groot voorbeeld voor me.

Dr. Berend Stolk, collega's verklaarden je voor gek toen je een ANIOS die eigenlijk kinderarts wilde worden aannam op jouw Intensive Care. Ik ben blij dat je dat gedaan hebt. Het was een fantastische tijd, en jij was zoveel meer dan een supervisor. Je was een voorbeeld, als clinicus, academicus en mens. Ik heb jouw gevleugelde lijfspreuk nog vaak ten harte genomen: "Protocollen zijn net lantaarnpalen. Ze geven licht in de duisternis, maar slechts een zot houdt zich er aan vast." Net wetenschap, eigenlijk.

Mijn paranimfen, Sander en Ronni, geweldig dat jullie dit met mij mee maken. Sander, sinds we als middelbare scholieren samen op het schooltoneel stonden, ben je een van mijn beste vrienden. Van Paradiso- tot Promotiefeestjes; het is vanzelfsprekend dat jij naast mij staat. Lieve Ronni, in het dankwoord van jouw proefschrift schreef je over onze eerste busrit waarin ik mijn levensverhaal vertelde, maar na vijftien jaar beste vrienden ben jij een van de hoofdrolspelers in dit verhaal. In die vijftien jaar ben je gegroeid van springerige, energieke en soms onzekere meid (Hoe vaak ik niet gehoord heb dat je het tentamen *zeker* niet gehaald heb… mrs. Cum laude!) tot een bewuste en zelfverzekerde moeder, echtgenoot en gepromoveerde (bijna-)radioloog. Het is ontroerend mooi dat allemaal van dichtbij mee te maken. Lieve vrienden, ik ben trots dat jullie mijn paranimfen zijn.

Natuurlijk ook dank aan alle vrienden waar ik mij gelukkig mee mag prijzen. De meeste ken ik al vele jaren en hebben mij zien verworden van kleine wijsneus tot grote wijsneus. In het bijzonder hier te noemen: Wouter, al vanaf ons vierde jaar hield jij van buiten spelen en ik meer van puzzelen. Onze vriendschap is zo bijzonder en hecht niet ondanks maar *omdat* we zo verschillen. Alden, heerlijk om de hectiek van het ziekenhuis even achter mij te laten door bij jou een biertje te drinken en te luisteren naar je enthousiaste verhalen over boeken, films, tv, muziek, *you name it*. Jij houdt mijn horizon breed. Martijn, ik bewonder je geloof en optimisme. Onze vriendschap en jouw gezin zijn me zo dierbaar dat het met gemak je emigratie naar Amerika gaat overleven. Ik kom je gewoon opzoeken! Gaat die roadtrip door de *Southern States* er dan toch van komen? Patrick, als ik je spreek is het direct gezellig. Dé eigenschap van een goeie vriendschap! Dyan, je staat altijd zo vanzelfsprekend voor mij klaar dat ik mij bijna bezwaard voel als ik weer iets te klussen heb. Je bent een toppertje!

Ik besef maar al te goed, ik zou niets bereikt hebben als ik niet zo'n veilige, mooie, liefdevolle en zorgzame omgeving had om in op te groeien. Een omgeving waar nieuwsgierigheid de ruimte kreeg, waar ik me veilig voelde om op ontdekkingstocht te gaan. Zo veel liefdevolle mensen hebben hieraan bijgedragen. Maar in het bijzonder, Lies en Wim. Jullie zijn zo veel meer dan tante en oom; jullie zijn mijn tweede ouderpaar, mijn tweede thuis. Nanke, 'ex-stiefmoeder' heeft wel heel veel negatieve connotaties bij elkaar, maar niets is minder waar: ik heb jouw oprechte liefde altijd gevoeld, en ik ben heel blij dat mijn broertje zo'n lieve, mooie moeder heeft. We boffen maar met je. Gera en Peter, jullie zijn de liefste schoonouders die ik mij kan wensen. Ik mag pas vijf jaar jullie mijn schoonouders noemen, maar het is toch al zo vanzelfsprekend natuurlijk om met jullie te zijn. Ik verheug me op alle mooie momenten in de toekomst die we als één familie gaan beleven.

Erik, lieve, grote, kleine broer. Wat je tegen me zei op mijn huwelijk in Nieuw-Zeeland (waar je de halve wereld voor overvloog om bij te zijn) was zó lief, daar kan ik hier niet tegen op. Anders dan: dat vind ik ook. Misschien omdat we halfbroers zijn, is onze broederliefde dubbel zo groot. Ik werk hard aan promotieboekjes en studies, maar jij werkt net zo hard aan je netwerk, eigen bedrijfje, managing-taken op Mallorca, en bent daarin minstens zo succesvol. Laat je niet tegenhouden door op schoolresultaten gefixeerde mensen, want je bent de meest breed-getalenteerde, sociale en ondernemende man die ik ken, en de liefste broer die ik kan wensen. Het gaat helemaal goed komen met jou. Ik ben trots op je.

Mama Marja en Papa Peter, lieve ouders. Als kind van gescheiden ouders die vrienden zijn gebleven is mijn vroegere gezinssituatie op z'n minst onconventioneel te noemen. Maar jullie hebben mijn belang altijd op de eerste plaats gezet, en daar ben ik jullie heel dankbaar voor. Daarom draag ik mijn proefschrift aan jullie op. Lieve pap, bij jou zijn was altijd een feestje. Het vanzelfsprekende waarmee je het je zonen naar hun zin maakt, is ontroerend. Dat vonden al mijn vriendjes ook; daarom wilden ze altijd bij jou logeren. Jij nam ons mee naar de dierentuin, musea, planetarium. Als echte journalist nam je mij dan mee in jouw nieuwsgierigheid; dat heeft de onderzoeker in mij los gemaakt. Lieve mama, jij bent er altijd voor mij geweest. Daar kan niets of niemand tegen op. Abraham Lincoln zei het mooi: "*All that I am, or hope to be, I owe to my angel mother.*"

Allerliefste Tamara, jij bent de liefde van mijn leven en het beste wat mij ooit is overkomen. Men zegt weleens "het recept voor een gelukkig huwelijk is een slecht geheugen", maar ik kan me nog heel goed onze ontmoeting herinneren bij het koffiezetapparaat van de onderzoekersvleugel, het uit de hand lopende lunchgesprek op het dakterras, de eerste borrel bij het Olympisch Stadion en de eerste date bij de Parade. Het was toen al zo fijn om bij je in de buurt te zijn, en het werd alleen maar beter. Bedankt dat je er voor mij bent; voor steun, voor samenspraak, of gewoon om samen van de mooie momenten van het leven

te genieten. We hebben al zo veel moois meegemaakt samen: verre reizen, opleidingen gestart of juist afgerond. Ik hoop nog heel veel moois met jou te mogen meemaken, en – wat ze ook zeggen over huwelijken en geheugens – ik zal altijd onthouden hoe mooi en lief jij bent.

CURRICULUM VITAE

Arend van Deutekom (sinds 6-12-2016: van Deutekom-Paff) is geboren op de heetste zomernacht van het jaar: 23 augustus 1984, te Amsterdam. Hij groeide op in de Kwakel, maar een echte 'Kwakelaar' werd hij nooit. Een VU'er werd hij wel, want nadat hij in 2002 *cum laude* zijn vwo-examen haalde op het Alkwin Kollege, Uithoorn, is hij gestart met zijn geneeskundestudie aan de Vrije Universiteit. Pas in 2016 is hij van de VU weg gegaan. Achtereenvolgens heeft hij daar behaald: zijn doctoraal geneeskunde (2006, cum laude), zijn geneeskundediploma (2008, cum laude) en zijn kinderartsendiploma (2016). Tijdens zijn opleiding tot kinderarts heeft hij onderzoek gedaan binnen de ABCD studie middels een door ZonMw gefinancierde AGIKO constructie. De resultaten van dit onderzoek zijn beschreven in dit proefschrift. Tijdens dit onderzoek behaalde hij zijn diploma voor de Masteropleiding Epidemiologie (VU 2014, cum laude).

Sinds mei 2016 is hij kinderarts – fellow kindercardiologie in het Academisch Medisch Centrum, Amsterdam.

Hij woont samen met zijn vrouw, Tamara Paff-van Deutekom.